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An unreadable (Unreadable) part(s) of the originally filed application documents has (have) been excluded from the publication.

(54) **Infection-resistant compositions, medical devices and surfaces and methods for preparing and using same.**

(57) A method of preparing an infection-resistant medical device comprising one or more matrix-forming polymers selected from the group consisting of biomedical polyurethane, biomedical silicones and biodegradable polymers, and antimicrobial agents, especially a synergistic combination of a silver salt and chlorhexidine (or its salts); also disclosed are medical devices having the synergistic composition therein or compositions thereon.

EP 0 328 421 A2

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Descripti n

Infection-Resistant Compositions, M dical Devices and Surfaces and Meth ds for Preparing and Using Sam

Background of the Invention

The present invention relates to infection-resistance compositions, medical devices and surfaces and to methods for using and preparing the same. This application is a continuation-in-part of U.S. Patent Application Serial No. 254,920, filed February 11, 1988.

Medical devices for use externally or internally with humans or animals can serve to introduce bacterial, viral, fungal or other undesirable infections. Certain prior art devices become unworkable after a short period of time, and must be replaced. In the case of urinary catheters, for example, frequent replacement can cause excessive discomfort to the patient and prolonged hospitalization. In the case of intravenous catheters used for critical care patients, infections can themselves prove life threatening. Additionally, there is always a threat of exposure to infectious contamination from surfaces that contact patients, from surgical gloves, and from other medical gear and apparatus.

To prevent such contamination, medical devices can be treated with an antimicrobial agent. Known methods of preparing an infection-resistant medical device have been proposed in U.S. Patents Nos. 3,566,874, 3,674,901, 3,695,921, 3,705,938, 3,987,797, 4,024,871, 4,318,947, 4,381,380, 4,539,234, and 4,612,337.

In addition, antimicrobial compositions useful as coatings for medical devices or for forming the device itself are disclosed in U.S. Patents Nos. 3,699,956, 4,054,139, 4,592,920, 4,603,152, and 4,667,143. However, such known methods are somewhat complicated or deficient in the results obtained. The art has great need for medical devices which are able to resist microbial infection when placed in the area of the body to which it is applied and which provide this resistance over the period of time which it remains in place. At the same time, these desirable characteristics must be achieved without sacrifice of other well recognized desirable characteristics. In the case of catheters, for example, it is important that any coating thereon leave a surface which provides a minimum of resistance to insertion of the catheter and which does not release a toxic substance to be adsorbed by the body.

Furthermore, some uses of antimicrobial metal compounds including silver salts in antimicrobial coatings for medical devices are known. Also, chlorhexidine and its salts are known to be powerful antiseptics, but the combination of chlorhexidine with silver nitrate has been shown to have prophylactic properties in burn therapy. In addition, the combination of chlorhexidine and sulfadiazine is known in topical applications to exhibit synergism against strains of Pseudomonas, Proteus, and Staphylococcus, as disclosed in Quesnel et al, Synergism between Chlorhexidine and Sulphadiazine, Journal of Applied Bacteriology, 1978, 45, 397-405.

Summary of the Invention

A principal object of the present invention is to provide an improved method of preparing an infection-resistant medical device which will impart antimicrobial activity to the medical device through a sustained and controlled activity rate over an appreciable period of time, without hampering the biocompatibility of the surface and other intended functions of the device. A further object of the present invention is to provide an infection- resistant medical device having superior antimicrobial properties.

Still another object of the present invention is to provide an antimicrobial composition useful in providing an antimicrobial coating on medical devices.

In accordance with the first embodiment of the present invention, there is provided a method of preparing an infection-resistant medical device which comprises

(a) preparing a coating vehicle by dissolving a matric-forming polymer selected from the group consisting of biomedical polyurethane, biomedical silicones, biodegradable polymers and combinations thereof in at least one solvent therefor;

(b) incorporating at least one antimicrobial agent in the coating vehicle to form a coating composition;

(c) coating a medical device with the coating composition; and

(d) drying the coating medical device.

It is preferred in the first embodiment that the antimicrobial agent be a combination of a silver salt and a biguanide and further preferred that the antimicrobial agent be a combination of a silver salt and a member of the group consisting of chlorhexidine and its salts. Also useful are chlorhexidine alone or in combination with nonoxynol 9, or pipracil as well as silver sulfadiazine in combination with nonoxynol 9.

In accordance with a second embodiment of the present invention, there is provided an antimicrobial composition comprising a mixture of (a) chlorhexidine and its salts, and (b) a silver salt.

Further, in accordance with a second embodiment of the present invention there is provided a method of preparing an infection-resistant medical device which comprises incorporating thereon or therein an antimicrobial agent comprising (a) a member of the group consisting of chlorhexidine and its salts, and (b) a member of the group consisting of silver and its salts.

The second embodiment of the present invention further provides an infection-resistant medical device having a coating thereon comprising (a) a member of the group consisting of chlorhexidine and its salts, and (b) a member of the group consisting of silver and its salts.

Another embodiment of the present invention still further provides a method for coating a medical device to provide an infection-resistant coating thereon which comprises the steps of:

(a) dissolving a matrix-forming polymer in a solvent therefor;

(b) dissolving an antimicrobial agent selected from the group consisting of chlorhexidine and its salts in a solvent which is miscible with the solvent polymer mixture prepared in step (a);

(c) dispersing a silver salt in one of the solutions prepared in (a) or (b);

(d) combining the solvent solutions and dispersions prepared in steps (a), (b) and (c) to provide a coating vehicle;

(e) applying the coating vehicle to the surface of the medical device; and

(f) drying the coated medical device.

In addition, the present invention provides an antimicrobial composition useful in applying an infection-resistant coating to medical devices which, in use, will exhibit a sustained activity rate over an appreciable time period.

Detailed Description of the Invention

Surfaces which may embody the present invention can be generally any surfaces that contact patients or are important in health care, including table tops, hospital beds and various specific medical devices. Medical devices are those for use both externally and internally and include, for example, urinary, both internal and external, and intravenous catheters, contraceptives such as condoms, medical gloves, such as surgical and examination gloves, wound dressings, drainage tubes, orthopedic, penile and other implants, wound clips, sutures, hernia patches and arterial grafts. The devices or surfaces, sometimes generally together referred to as "surfaces" herein, can be made of a variety of natural or synthetic materials such as metals, plastics and polymers, and including Dacron®, rubber, latex, collagenous substances, silicone, polyurethane, polyvinyl chloride, Teflon®, polypropylene, polyethylene, poly(lactic acid), polyglycolic acid, cotton, silk, stainless steel, porous ceramics, and porcelain.

Definitions

The following specification refers to a number of microorganisms in describing the invention or its use. Unless otherwise stated, the following are the generally recognized names of the microorganisms, together with their source:

Organism	Source
Staphylococcus aureus	clinical isolate-Columbia Presbyterian Hosptial New York, New York
Staphylococcus epidermidis	clinical isolate-Columbia Presbyterian Hosptial New York, New York
Esherichia coli	clinical isolate-Columbia Presbyterian Hosptial New York, New York
Candida albicans	ATCC No. 11651

It is also noted that unless otherwise stated, the concentrations and ranges expressed as percentages (5), indicates the respective value based on weight of solid per volume of solvent. As an example, a 1% polyurethane in a solvent coating vehicle comprising tetrahydrofuran (THF) represents 1 gram of polyurethane in 100 ml of THF. On the other hand, in expressing relative proportions of two or more solvents in a coating vehicle, the percentages given are on a vol/vol basis.

Polymeric Coating Agent

The polymeric coating agent component of the coating vehicle of the present invention is selected from the group consisting of biomedical polyurethanes, biomedical silicones, biodegradable polymers and combinations thereof. It has been found that these particular polymeric materials enable the antimicrobial agent of the second embodiment of the invention to be retained and released in an active state on the coated medical device over an appreciable period of time, e.g., from about 12 to in excess of 21 days.

Selection of the coating vehicle depends upon the specific composition of the surface of the device to be coated, and the characteristics sought. For example, a polyurethane catheter is preferably coated with a formulation based on a biomedical polyurethane matrix-forming material. A silicone rubber catheter, on the other hand, preferably is provided with a coating having a silicone rubber as a matrix-forming material. It has

also been discovered that a final thin coat of a silicone fluid after a first coating of biomedical polyurethane or of silicone rubber imparts surface glossiness and lubricity to the catheter. Thus, multiple, combined coatings, described in greater detail below, can also be achieved with improved characteristics.

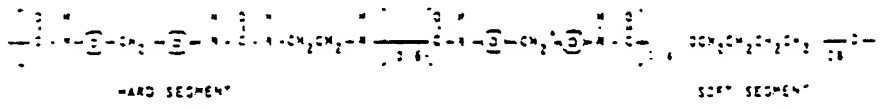
In addition to polymeric coating compositions, the antimicrobial compositions of this invention may be applied to surfaces of medical devices in powder form, preferably under conditions which cause adherence of the powder to the surface of the device. For example, medical gloves, such as surgical or examination gloves fabricated from latex, polyurethane or polyvinyl acetate, may be coated with a powder containing the antimicrobial composition, as will be explained below in more detail.

A. Biomedical Polyurethane

In accordance with the first embodiment of the invention, the essential polymeric coating agent component of the coating vehicle is biomedical polyurethane, since it has been found unexpectedly that polymeric materials of this class enable the antimicrobial agent to be retained in an active state on the coated medical device and released over an appreciable period of time, e.g., from about 12 to in excess of 21 days, without altering the biocompatibility, lubricity and non-thrombogenicity of the surface. Suitable biomedical polyurethanes include both the ether-based polyurethanes and the ester-based polyurethanes described on pages 175-177 of Controlled Release of Biologically Active Agents, by Richard W. Baker, John Wiley and Sons, 1987; the ether-based compounds are preferred. A thorough discussion of a number of proprietary biomedical polyurethanes is found in Polyurethanes in Medicine, by Michael D. Lelah and Stuart L. Cooper, CRC Press, Inc., Fla 1986, pp. 57-67.

The following is a listing of proprietary biomedical polyurethanes that are useful in accordance with the invention:

1. Biomer®, which consists of 4,4'-diphenylmethane-diisocyanate (MDI) and low molecular weight polytetramethyleneoxide (PTMO) segments with diamines as chain extenders. A proposed repeat unit chemical structure for Solution Grade Biomer® is:



2. Acuthane® is a block copolymer which contains 10% polymethylsiloxane and 90% polyetherurethane.

3. Pellethane® is an aromatic ether polyurethane. Pellethane® 2363 (80AE) is not crosslinked and is readily soluble in dimethylacetamide, tetrahydrofuran, or N-ethyl pyrrolidone. The 90A of the same series contains crosslinks due to the excess of isocyanates present during the polymerization process and is therefore more difficult to solubilize.

4. Rimplast® is a silicone urethane made with either aliphatic or aromatic ethers or esters of polyurethane and a reactive, high molecular weight silicone to form an interpenetrating network (IPN).

We have found that best results are obtained using Pellethane® 2363-80AE, one of a series of thermoplastic, segmented elastomers sold under the designation Pellethane® by Dow Chemical Co. These materials are described at p. 60 of Lelah et al, supra. Another suitable product is Biomer®, which is conveniently available as a 30 wt.% solution in N, N-dimethylacetamide (DMAC) described at pp. 57-58 of Lelah et al, supra. Another suitable material is Rimplast®, a series of biomedical urethanes containing silicones, reacted to form a series of interpenetrating network modified silicones containing polyurethanes. A description of these materials are found on pp. 61-63 of Lelah et al, supra.

The prior art, such as U.S. 4,667,143, fails to distinguish between various polymeric coating agents. The patent states that any one of a long list of resins may be mixed with an antimicrobial metal compound to provide antimicrobial coatings on medical devices. The working examples of the patent utilize either ABS polymers or alkoxy curing RTV silicone rubbers. Quite unexpectedly we have found that the specific application of biomedical polyurethanes as a coating agent is superior to all other known polymeric coating materials. This discovery was made by first determining the relative solubilities of various polymeric coating agents in equal amounts of DMAC and ethylacetate. The results of this screening test are shown in Table I.

TABLE I

Solubility of Various Polymers in Solvent Comprising 50% DMAC + 50% Ethyl Acetate

1.	POLY (ETHYLENE)	NS
2.	POLY (METHYL METHACRYLATE)	S
3.	POLY (ETHYLENE-MALEIC ANHYDRIDE)	NS
4.	POLY (CAPROLACTONE)	S
5.	POLY (VINYL ALCOHOL) MW 25,000	NS
6.	POLY-3-HYDROXYBUTYRATE $5x10^5$	NS
7.	POLY (ETHYLENE OXIDE) MW 4,000,000	NS
8.	POLY (BUTANEDIOL-1, 4-TERE-PHTHALATE)	NS
9.	POLY (HEXAMETHYLENE DODECANEDIAMIDE) NYLON	NS
10.	POLY (VINYL ACETATE) MW 500,000	S
11.	POLY (VILIDENE CHLORIDE-ACRYLONITRILE) 80:20	S
12.	POLY (HEXAMETHYLENE SEBACAMIDE) NYLON	NS
13.	POLY (PROPYLENE, ISOTACTIC)	NS
14.	POLY (ETHYL METHACRYLATE)	S
15.	POLY (STYRENE-MALEIC ANHYDRIDE)	S
16.	POLY (STYRENE ALLYL ALCOHOL)	S
17.	POLYACRYLAMIDE	NS
18.	POLY (ISO-BUTYL METHACRYLATE)	S
19.	POLY (VINYL PYRROLIDONE)	S
20.	POLY (PROPYLENE, CHLORINATED, 65%)	S
21.	POLY (N-BUTYL METHACRYLATE-ISO-BUTYL METHACRYLATE 50/50)	S
22.	POLY (VINYL CHLORIDE-VINYL ACETATE)	S
23.	POLY (ACRYLIC ACID) MW 4,000,000	NS
24.	POLY (HEXAMETHYLENE ADIPAMIDE)	NS
25.	POLY (N-BUTYL METHACRYLATE)	S
26.	POLY (CARBONATE BISPHENOL A)	NS
27.	POLY (LAURYL LACTIM)	NS
28.	POLY (CAPROLACTAM)	NS
29.	POLY (ACRYLAMIDE-ACRYLIC ACID SODIUM SALT) 70% CARBOXYL HIGH CARBOXYL MW 200,000	NS
30.	POLY (VINYL ALCOHOL) 88% MOLE HYDROLYZED, MW 25,000	NS
31.	POLY (ACETAL) RESIN	NS
32.	POLY (STYRENE-ACRYLONITRILE 75:25)	S
33.	POLY (METHYL VINYL ETHER/MALEIC ANHYDRIDE)	NS
34.	POLY (SULFONE) RESIN	S
35.	POLY (VINYLDIENE FLUORIDE)	S
36.	POLY (TETRAFLUOROETHYLENE)	NS
37.	POLY (VINYLDIENE CHLORIDE/VINYL CHLORIDE 86:12)	S
38.	POLY (VINYL BUTYRAL) MW 100,000-150,000	S
39.	POLY (p-VINYL PHENOL)	S
40.	POLY (ETHYLENE-ACRYLIC ACID 92:8)	NS
41.	POLYURETHANE (DOW PELLETHANE® 2363-80AE)	S

S = READILY SOLUBLE NS - NOT SOLUBLE

After rejecting the insoluble polymers, steps were taken to coat the soluble polymers, i.e., those identified in Table I as numbers 2, 4, 10, 11, 14, 15, 16, 18, 19, 20, 21, 22, 25, 32, 34, 35, 37, 38, 39, and 41, upon catheters to determine which formed stable, workable coatings. Both urinary and I.V. catheters were used, and for this test, the urinary catheter was fabricated of latex and the I.V. catheter of Pellethane® 2363, 90A, described above.

Two different coating formulations were used having the following formulations:

1. 1% chlorhexidine acetate (CHA) + 6% polymer in a solvent consisting of 50% DMAC + 50% ethyl acetate (EA)
2. 2% CHA + 6% polymer in a solvent consisting of 50% DMAC + 50% EA

The key characteristics of glossiness, smoothness, and stickiness of the exposed coating surface as well as the degree of adhesion of the coating to th catheters surfaces of the coated polymers were then compared, and the results are shown in Table II.

TABLE II

Quality of Coating on the Polyurethane Catheter (I.V.) and the Latex (URO) Urinary Catheter

	IV GLOSSINESS	URO GLOSSINESS	IV SMOOTHNESS	URO SMOOTHNESS	IV STICKINESS	URO STICKINESS	IV ADHESION	URO ADHESION
2	YES	YES	YES	YES	SLIGHT	YES	GOOD	POOR
4	SEMI	SEMI	YES	YES	NO	NO	GOOD	GOOD
10	YES	YES	YES	YES	NO	NO	GOOD	POOR
11	SEMI	SEMI	NO	NO	NO	NO	GOOD	POOR
14	SEMI	SEMI	YES	YES	SLIGHT	NO	GOOD	POOR
15	YES	YES	YES	YES	NO	NO	GOOD	GOOD
16	YES	YES	YES	YES	NO	NO	GOOD	GOOD
18	NO	NO	YES	YES	NO	NO	GOOD	GOOD
19	YES	YES	YES	YES	YES	YES	GOOD	GOOD
20	SEMI	NO	YES	YES	SLIGHT	NO	GOOD	GOOD
21	NO	NO	YES	YES	SLIGHT	NO	GOOD	GOOD
22	YES	YES	YES	YES	YES	NO	GOOD	POOR
25	NO	NO	YES	YES	YES	NO	GOOD	GOOD
32	YES	YES	YES	YES	YES	NO	GOOD	POOR
34	NO	NO	MEDIUM	YES	NO	SLIGHT	GOOD	POOR
35	NO	NO	YES	YES	YES	YES	GOOD	POOR
37	SEMI	NO	YES	MEDIUM SMOOTH	YES	YES	GOOD	FAIR
38	NO	SEMI	NO	YES	YES	YES	GOOD	POOR
39	YES	SEMI	YES	YES	SLIGHT	NO	GOOD	GOOD
41	YES	YES	YES	YES	NO	NO	GOOD	GOOD

Coating Formulas: URO = 6% Polymer + 1% CHA in $\frac{50}{50}$

I.V. = 6% Polymer + 2% CHA in $\frac{50}{50}$

Thus, although several polymers can be used as controlled delivery matrices, biomedical polyurethane, number 41 in Table II, was found to possess across-the-board superior characteristics.

Glossiness, smoothness, and stickiness of the exposed coating surface as well as adhesion of the coating to the device are crucial characteristics. Equally important to the invention is the coating agent's ability to absorb and release, in a controlled-dosing manner, bio-active agents. Again, biomedical polyurethane was far superior, and the results are shown in Table III, below. For this comparison, chlorhexidine diacetate (CHA) was incorporated into solutions of each of the polymers found to be soluble as listed in Table I.

TABLE III

Comparative Matrices Days of Activity

POLYMER MATRIX SYSTEM	I.V.	URO
1. POLY (METHYL METHACRYLATE)	3	NT
2. POLY (CAPROLACTONE)	3	NT
3. POLY (VINYL ACETATE) MW=500,000	2	NT
4. POLY (VINYLDIENE CHLORIDE-ACRYLONITRILE) 80:20	1	NT
5. POLY (ETHYL METHACRYLATE)	2	NT
6. POLY (STYRENE-MALEIC ANHYDRIDE)	0	0
7. POLY (STYRENE ALLYL ALCOHOL)	1	1
8. POLY (ISO-BUTYL METHACRYLATE)	2	2
9. POLY (VINYL PYRROLIDONE)	2	2
10. POLY (PROPYLENE, CHLORINATED, 65%)	2	2
11. POLY (N-BUTYL METHACRYLATE-ISO-BUTYL METHACRYLATE) 50/50	2	2
12. POLY (VINYL CHLORIDE-VINYL ACETATE)	2	NT
13. POLY (N-BUTYL METHACRYLATE)	1	2
14. POLY (STYRENE-ACRYLONITRILE 75:25)	2	NT
15. POLY (SULFONE) RESIN	1	NT
16. POLY (VINYLDIENE FLUORIDE)	1	NT
17. POLY (VINYLDIENE CHLORIDE/VINYL CHLORIDE) 88:12	1	2
18. POLY (VINYL BUTYRAL) MW=100,000-150,000	3	NT
19. POLY (p-VINYL PHENOL)	1	0
20. POLY (URETHANE) DOW PELLETHANE®	>4	>4
21. PTUE 205 RIMPLAST®	3	3

I.V. = intravenous catheter fabricated of Pellethane® 2363, 90A

URO = urinary catheter fabricated of latex

NT = not tested due to poor film formation or lack of adhesion of coating to substrate.

The coating formulas used in preparing coating vehicles for Table III were:

1. Urinary Catheters: 1% CHA + 6% Polymer in solvent.
2. I.V. Catheters: 2% CHA + 6% Polymer in solvent.

In both cases, the solvent consisted of 50% dimethylacetamide and 50% ethyl acetate.

The results given in Table III were obtained using the following bioassay:

1. Latex Urinary Catheters: 2 cm. sections were soaked in 5cc of Trypticase Soy Broth (TSB) and challenged with 10^4 CFU of a 1:1 mixture of Staph. epidermidis and E. coli pre-diluted to 0.3 optical density at 600 nm.
2. Polyurethane I.V. Catheters: 2cm. sections thereof were soaked as above and challenged with 10^4 CFU of Staph. aureus, again pre-diluted to 0.3 optical density at 600 nm.

This was a severe test, where the catheters were challenged daily with a broth culture having 10^4 CFU of the bacteria. The results show superior performance of biomedical polyurethane in maintaining sustained activity for more than four days for both types of catheters when coated with Pellethane® 2363 (line 21) and three days for Rimplast® PTUE 205, a silicone IPN modified urethane. The other resins averaged only one to two days.

The superior characteristics of the biomedical polyurethanes, lines 20 and 21, are surprising, since the prior art does not hint or suggest that any one of the above polymer matrices is any better than any other. Instead, the art teaches a general and uniform performance from each.

As a consequence of these results, several factors are postulated to account for the superior performance of biomedical polyurethane.

Polymer Backbone Rotational Flexibility:

It is well established that apart from the molecular weight of a solute, solubility in a polymer depends on the ability of the backbone of that polymer to rotate about one or more axes. Polyurethane's backbone flexibility falls somewhere in between the extreme freedom of rotation found in the silicone rubbers to the inflexibility of polystyrene. Since polyurethane is a segmented block copolymer made of both hard and soft segments it combines the ability of readily releasing bio-active agents from the amorphous phase with the slow release, reservoir-like characteristics of the hard or crystalline domain. Intramatrix diffusion probably occurs as the bio-active drug levels in the soft domains drop, causing a gradient related flow of solute out of the crystalline phase into the more flexible areas which then in turn diffuses out into the environment.

Progressive Formation of Interconnected Diffusion Channels:

As the drug molecules at the surface of the matrix are dissolved, the solute (blood, perspiration, saline, media etc.) is allowed to penetrate into the film, thus forming micro-channels which further facilitate the release process. The pore formation is likely proportional to the flexibility of the backbone of the polymer, whereby the rate of channeling falls as the domain becomes more crystalline.

Polyurethane has, on the average, 75 to 100 times the water absorption of silicone (RTV) and 25 times that of polystyrene. The greater value for polyurethane is probably due to the hydrophilic nature of the soft segment and presumably means that channel formation is enhanced.

Electrical Properties of the Matrix:

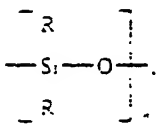
The charge that a polymer carries influence the affinity of the antimicrobial agent for the matrix. In some cases, such as when the antimicrobial agents silver (Ag) or chlorhexidine acetate (CHA) are mixed with latex, the binding is so strong that ions of the antimicrobial agent are restricted in their ability to diffuse out of the matrix. Some biomedical polyurethanes carry a positive charge and therefore do not react with, and thus inactivate, cationic antimicrobial agents such as Ag or CHA. Anionic compounds such as piperacillin or sulfadiazine are relatively unreactive and extremely soluble so that they do not bind to polyurethane and are released at a steady and prolonged rate.

Thus, the polymeric coating agent component cannot be polyethylene vinyl acetate, polyvinyl chloride or polyvinyl alcohol, because such polymers give unsatisfactory results. As mentioned above, the polymer of choice is a polyether polyurethane and, more specifically, Pellathane® 2363-80AE. It has been further found that this polymer in solvent must critically range from 1-10%, and preferably 2-6%, and most preferably 3% by volume, for best performance.

B. Biomedical Silicones

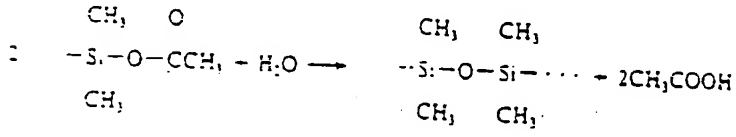
Suitable biomedical silicones include the silicone rubbers or elastomers described on pp. 156-162 of Controlled Release of Biologically Active Agents, by Richard W. Baker, John Wiley and Sons, 1987.

Silicone rubbers having the general formula

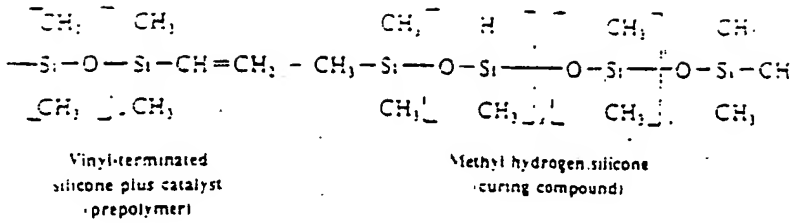


where R is either a methyl of a $-C_6H_6$ substituent, are useful. More specifically, the following proprietary biomedical silicones may be used:

1. Silastic® Type A Medical Adhesive, a polydimethyl siloxane sold by Dow Corning and which is a one component system which cures at ambient room temperature and humidity. Its formula is:

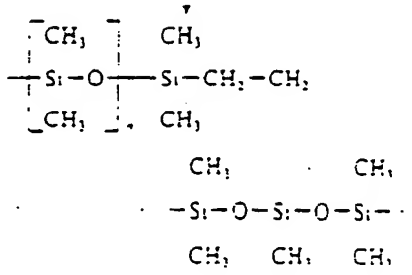


2. Other Silastic® products that can be used to form time release matrices include:
   (a) Q72213 - a medical grade dispersion of silicone in trichloroethane;
   (b) Silastic® 360; and
   (c) MDX4-4159, a proprietary product of Dow Corning containing 50% of an amino functional polydimethyl siloxane copolymer and 50% of mixed aliphatic and isopropanol solvents.
3. Two component vinyl curing silicone - a dimethyl silicone compound with a vinyl terminated prepolymer component is reacted to the backbone of a second silicone component.

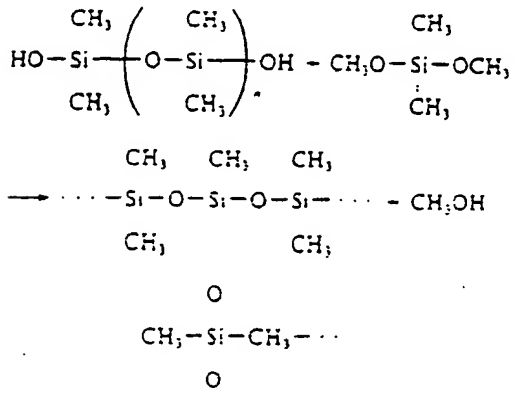


Vinyl-terminated silicone plus catalyst (prepolymer)

Methyl hydrogen silicone (curing compound)



4. Two component curing silicone - Silastic® 382 is an example of a silicone which cures by condensation whereby a prepolymer containing a hydroxy group is crosslinked by the addition of a methoxysilane and catalyst.



It is preferred to employ room temperature curing materials. It is also preferred to employ a mixture of equal parts of a polydimethyl siloxane such as Silastic® Type A adhesive and a mixed amino functional polydimethyl siloxane copolymer such MDX4-4159 in mixed aliphatic and isopropanol solvents, to provide a coating surface having a smooth surface and extended period of activity.

The selection of specific polymeric coating agent to form a coating matrix will depend upon the nature of the surface to which the coating will be applied. It is preferred that a biomedical polyurethane be applied to a polyurethane surface to assure good coating adherence. A biomedical silicone, such as a mixture of Silastic® Type A Medical Adhesive and MDX4-4159, is suitable to coat a device that is fabricated of silicone, polyurethane of of latex.

C. Biodegradable Polymers

It has further been found that use of a biodegradable polymer in the coating composition of this invention, either alone or in combination with one or more of the other biomedical polymers, enhances the character of the polymer matrix. Suitable biodegradable polymers include the homopolymers poly(glycolic acid), poly(D-lactic acid), poly(D,L-lactic acid), poly(D,L-ethylglycolic acid), poly(dimethylglycolic acid), poly(D, L-methylethylglycolic acid), and poly(E-caprolactone), as well as biodegradable polyhydroxy butyric acid and mixtures thereof. A preferred biodegradable polymer is polylactic acid (PLA).

Thus biodegradable polymer may be added to biomedical polyurethane in the quantities indicated herein. The biodegradable polymer modulates the rate of release of antimicrobial drugs. The initial burst of drug which occurs during the first few days after implantation is more or less eliminated since the drug is bound in the biodegradable polymer and will be released only when degradation of the polymer occurs. Inclusion of a biodegradable polymer such as PLA in the matrix gives prolonged biocidal activity as confirmed in in vitro studies, shown in Table IV, below.

TABLE IV

Enhanced Efficacy of Polyurethane + PLA Matrix

Coating Composition	Days of Activity*
1. 3% DPU + 3% CHA	4
2. 3% DPU + 1% PLA + 3% CHA	6
3. 3% DPU + 1% AgSD + 1% CHA	4
4. 3% DPU + 1% PLA + 1% AgSD + 1% CHA	5

DPU = Pellethane® 2363-80AE - Dow Chemical Co.

PLA = poly (lactic acid) molecular weight of 100000

AgSD = silver sulfadiazine

CHA = chlorhexidine diacetate

Solvent = 25 parts of ethanol and 75 parts of tetrahydrofuran (THF)

* determined according to the bioassay set forth above with regard to Table III

An additional advantage of using a biodegradable polymer such as PLA in a polyurethane matrix is to allow improved tissue ingrowth simultaneously with a prolonged antimicrobial effect as the biodegradable polymer degrades. Thus, this embodiment of the invention is particularly important in orthopedic applications as well as in such devices as arterial grafts where there is a need for formation of the pseudo-intima or the growth of tissue into the interstices of orthopedic implants and arterial grafts, as well as cuffs which anchor IV catheters in place.

Suitable biomedical poly(lactic) polymers include the poly(L-lactide), poly (D-lactide) and the poly(D-L-lactic acid). These materials are described, inter alia, on pp. 87, 88 and 115, of Baker, supra, and are biodegradable. Poly(L-lactic) acid is preferred, and those polymers having a range of molecular weights ranging from 2000 to 300.000 have been used with success.

The poly(lactic acid) polymers are bioerodable, and while they can be used alone, it is preferred that they be combined with either a biomedical polyurethane or a biomedical silicone.

As in the first embodiment of the invention, an additional advantage of using PLA in a polyurethane matrix is to allow improved tissue ingrowth simultaneously with a prolonged antimicrobial effect as the PLA degrades.

Thus, this embodiment of the invention is particularly important in orthopedic applications as well as in such devices as hernia patches and arterial grafts where there is a need for formation of the pseudo-intima or the growth of tissue into the interstices of orthopedic implants and arterial grafts, as well as cuffs which anchor I.V. catheters in place.

Solvents

The solvents used in preparing the coating vehicle used in the present invention includes solvents for the biomedical polymeric coating agent and/or the antimicrobial agent, and include acetic acid, methyl acetate, ethyl acetate, hexane, N-N-dimethylacetamide (DMAC), tetrahydrofuran (THF) , alcohols (e.g., alkanols), water, N-ethyl-2-pyrrolidone (NEP), n-(2-hydroxy-ethyl)-2-pyrrolidone, n-cyclohexyl-2-pyrrolidone and combinations thereof. The selection of a particular solvent or mixture of solvents will depend upon the specific biomedical polymeric coating agent being used as well as upon the particular antimicrobial agent or combination of agents.

Certain desired solvents for the polymeric coating agent may not be good solvents for an antimicrobial agent of choice. In that case, a solvent is selected which will dissolve the antimicrobial agent and will be miscible with the solvent solution of polymeric coating agent. Thus, a solvent solution of the antimicrobial agent may be combined with the biomedical polyurethane in solution in its solvent and the two solutions thereafter combined to form a uniform mixture.

Another important consideration in selecting a solvent is that the resulting solution will readily adhere to and form a film on the surface to which it is applied. Certain solvent solutions containing certain polymers do not adequately wet latex surfaces, for example, with the result that the coating is discontinuous or non-adherent.

In a preferred coating mixture where it is desired to incorporate chlorhexidine acetate with a biomedical polyurethane as coating agent, a preferred solvent is the combination of ethanol and THF, preferably in the proportions of 10% ethanol and 90% THF. Good results have been obtained where this combination contains from 1 to 25% ethanol. Another preferred combination for use with chlorhexidine acetate is NEP and THF, over a range of 1.0 to 10% NEP, more preferably 5%. Still further useful combinations of solvents include DMAC and ethyl acetate, containing from 1 to 50% DMAC, and DMAC and THF, with 1 to 25% DMAC. Each of these preferred solvent combinations results in a coating vehicle which readily wets and adheres to surfaces of medical devices fabricated from medical polyurethane, latex and/or silicone polymer, but also provides a superior adherent coating.

Antimicrobial Agents

Antimicrobial agents useful according to this first embodiment of the invention include the biguanides, especially chlorhexidine and its salts, including chlorhexidine acetate, chlorhexidine gluconate, chlorhexidine hydrochloride, and chlorhexidine sulfate, silver and its salts, including silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine, polymyxin, tetracycline, aminoglycosides, such as tobramycin and gentamicin, rifampicin, bacitracin, neomycin, chloramphenicol, miconazole, quinolones such as oxolinic acid, norfloxacin, nalidixic acid, pefloxacin, enoxacin and ciprofloxacin, penicillins such as oxacillin and pipracil, nonoxynol 9, fusidic acid, cephalosporins, and combinations thereof.

From the above list, unexpectedly, some special combinations have been found. The combination of the biguanides, especially chlorhexidine and its salts with silver salts cause a special synergistic sustaining of antimicrobial action, as described in the second embodiment of the invention below. The biguanides are also synergistically effective with nalidixic acid and its derivatives. Another effective combination is chlorhexidine acetate and pipracil.

Where the antimicrobial agent used is insoluble in the coating vehicle, as is the case with most of the silver salts and the water insoluble chlorhexidine, it is preferred that the agent be very finely subdivided, as by grinding with a mortar and pestle. A preferred product is micronized, e.g., a product wherein all particles are of a size of 5μ or less. In the case of the preferred silver sulfadiazine, a micronized product may be used.

The antimicrobial agent is preferably employed in the coating vehicle at a level such that the final coating contains from 10 to 70% by weight of the antimicrobial agent. This may be accomplished by providing a concentration of, for example, 0.5 to 3%, preferably 1%, of chlorhexidine acetate and 0.5 to 5%, preferably 1%, of silver sulfadiazine in the coating vehicle.

Unique to the invention is the use of chlorhexidine since such use internally, that is, in the human body, is heretofore unknown. Though there are examples available on the use of chlorhexidine in the bladder, such data is not relevant hereto, since it is not truly an internal use as there is no contact with the patient's circulation.

The absence of even a hint of using chlorhexidine internally is due, at least in part, to its relatively high toxicity and chemical nature (highly polar, reactive, high affinity for lipids and proteinaceous materials), leaving it a poor candidate as a systemic drug. The only way to use chlorhexidine internally is in the time release matrix system described above that allows for a dose that is non-toxic to the patient but effective against microorganisms.

Coating Vehicle

The coating vehicle is prepared according to the invention by dissolving the polymeric coating agent in a solvent therefor and by combining this solution with a solution or suspension of the antimicrobial agent. These materials can be combined at room temperature or at a slightly elevated temperature with the aid of agitation. It is preferred to employ solvents with readily evaporate from the coating at room temperature, or at an elevated temperature below that which inactivates the antimicrobial agent.

In the case of a preferred antimicrobial composition chlorhexidine acetate, either alone or in combination with silver sulfadiazine, the coating vehicle is prepared by first dissolving the polymeric coating agent such as the biomedical polyurethane in a solvent therefor, such as tetrahydrofuran (THF). The chlorhexidine is then dissolved in a solvent therefor, such as ethanol, water, or preferably N-ethyl-2-pyrrolidone (NEP), which is also miscible with THF.

Other Agents in Coating Matrix

In addition to antimicrobial agents and matrix forming materials, the coatings of the present invention may contain other compatible ingredients to advantage. For example, where anti-blood clotting activity is desired, heparin may be used, preferably at a level of 0.2%. Another useful ingredient is dextran sulfate, preferably also at a level of 0.2%

In accordance with the method of this invention, the medical device can be coated with the coating composition by known coating techniques, such as dip coating, spray coating, brush coating, roller coating, etc. Moreover, multiple coatings using the same or different polymer matrix-forming agents for each, can be used.

The coated medical device can be dried at room temperature to remove solvent or with the aid of a slightly elevated temperature over an appropriate time period.

The coating method can be repeated to build up a thicker coating on the medical device and/or to use a different antimicrobial agent in each coating, if desired.

In accordance with another preferred embodiment of the invention, the antimicrobial composition of this invention comprising a mixture of a biguanide and a silver salt in powder form is applied directly to the surface of a medical device. The method of application is one which assures adherence of the powder to the surface. One such method applies the powdered antimicrobial agent to an adhesive surface in micro layers so that minimum loss of adhesiveness occurs while imparting a high level of protection against growth of microorganisms to the surface. Other procedures include mixing the powder with adhesive prior to its application, and providing areas on the surface which alternatively contain adhesive and powdered antimicrobial agent. In one preferred method, a powder comprising a mixture of biguanide and a silver salt, most preferably a mixture of silver sulfadiazine and chlorhexidine acetate, was applied to rubber gloves at a point during their manufacture when the rubber was soft and/or semi-molten. The powder was found to adhere well after cooling of the gloves to room temperature.

It will further be understood that the invention does not require coating both the inside and outside of medical devices, especially catheters. In fact, it has been found that some catheters coated only on the outside provide necessary prophylaxis, without chemical or biological interference with the materials added to the body by the catheter. There may be instances when, for example, a coating containing an antimicrobial agent and heparin is applied only on the outside of an I.V. catheter used for providing blood to a patient. In other instances, it is advantageous to apply a coating with the anti-coagulent on the inside of the catheter to prevent clotting blockages. These specific selections are all within the scope of the invention.

Concentrations of the coating vehicle, the antimicrobial composition, the coating composition and resultant coating can be selected as desired and as illustrated by the following representative examples. In the case of the preferred combination of chlorhexidine acetate and silver sulfadiazine, good results have been obtained when the agents are present in a proportion ranging from 1:9 to 9:1, respectively. Further, it is preferred that this combination of antimicrobial agents be present at levels of from 10 to 70% by weight of the final coating.

The invention will be further illustrated by the following examples. Unless indicated otherwise, the silver sulfadiazine (AgSD) used in the examples was a micronized powder product having a particle size of 5μ or less.

It is recognized, however, that silver or its salts, including silver sulfadiazine, having a larger average particle size are useful according to this invention, and particle size selection will depend on the contemplated use of the medical device.

Example 1

A coating vehicle for use in accordance with the present invention was prepared as follows:

1 gm of chlorhexidine acetate (CHA) was added to 5 cc of N-ethyl-2-pyrrolidone (NEP). The mixture was heated to 50-60°C and agitated in a Vortex® stirrer until the CHA dissolved.

10 cc tetrahydrofuran (THF) was then added to the CHA solution in NEP and the mixture thoroughly agitated to form a uniform solution.

3 gm of Pellethane® 2363-80AE of the Dow Chemical Co. was added to 50 cc of THF. The mixture was warmed to about the boiling point of THF, 65-70°C, and stirring with a Vortex® stirrer was continued until the

polyurethane was dissolved.

1 gm of silver sulfadiazine (AgSD) powder was suspended in 35 cc of THF and vigorously agitated in a Vortex® stirrer to form a uniform suspension. The CHA solution in NEP and THF prepared above was then combined with the polyurethane solution and agitated to form a clear solution. As a last step in preparing the coating vehicle, the AgSD suspension in THF was added and the entire mixture agitated to maintain a uniform suspension. Thus was provided a coating vehicle containing 1% CHA and 1% AgSD as antimicrobial agents, together with 3% of the biomedical polyurethane. The solvent in this case was a mixture of solvents comprising 5% NEP and 95% THF. The CHA was in solution in the coating vehicle, while the AgSD was in uniform suspension.

The coating vehicle prepared above was used to coat an I.V. catheter fabricated of Pellethane® 2363-90A. The catheter was dipped in the coating vehicle while the vehicle was being continuously agitated to insure a uniform suspension. The coated catheter was then dried. A tightly adherent coating on the catheter was thus provided. A bioassay of sections of the catheter performed in accordance with the test given above with respect to Table III showed sustained activity against the microorganisms for in excess of eight days.

Example 2

Methods of Preparing I.V. and Urinary Catheters Coated with Soluble Silver Salts and Water Insoluble Chlorhexidine

In certain instances, it is necessary to use antimicrobial agents starting in solution rather than as comminuted solids. Though the invention comprises both, coating with the precursors of certain antimicrobial agents in solution has been found to be best achieved in one of two ways:

Method 1

Coating vehicle contains 1% $AgNO_3$ + 1-3% water insoluble free-base chlorhexidine + 6% polyurethane in DMAC/ethyl acetate mixture (1:1).

Water insoluble chlorhexidine is first prepared by precipitating the chlorhexidine from chlorhexidine acetate. This chlorhexidine is used for coating purposes in those instances where the chlorhexidine salts are reactive with other ingredients of the coating vehicle. For example, the acetate or gluconate salts of chlorhexidine react with silver nitrate instantly in aqueous solutions with the undesired result that each is inactivated.

Preparation of 100ml coating vehicle.

1 gm silver nitrate and 1gm water-insoluble free-base chlorhexidine were dissolved separately in 10ml portions of DMAC. 6gm polyurethane, Pellethane® 2363-80AE, were dissolved in 30ml DMAC and mixed with the silver nitrate and chlorhexidine solutions. 50ml ethyl acetate was mixed with this solution to form a coating vehicle and used for coating.

Method 2

Coating vehicle contains 0.3% $AgNO_3$ + 0.75% sulfadiazine + 1-2% chlorhexidine + 6% polyurethane in DMAC/ethyl acetate mixture (1:1).

The method of preparation of this coating solution is the same as described in Method 1 except that the sulfadiazine is added to the chlorhexidine solution and a uniform dispersion formed. The medical device (e.g., catheter) is dipped, sprayed or painted, at least once, with this solution.

A series of catheters were coated with the coating solutions prepared by methods 1 and 2 in this example and compared with a commercially available catheter coated with silver oxide. Catheters numbers 2 and 6 were prepared in accordance with method 1 above. Catheters numbers 3, 5 and 7 were prepared by method 2 above. Catheters numbers 1 and 4 were prepared in accordance with the method and using the formulation following Table I, the chlorhexidine in catheter 4 being the water insoluble type referred to in method 1 above.

The tests recorded in Table V are described elsewhere in this specification. The activity in trypticase soy broth (TSB) was determined by the bioassay described as follows:

1. Latex Urinary Catheters: 2 cm sections were soaked in 5 cc of Trypticase Soy Broth (TSB) and challenged with 10^4 CFU of a 1:1 mixture of Staph. epi and E. coli pre-diluted to 0.3 optical density at 600 nm.

2. Polyurethane I.V.: 2 cm sections soaked as above and challenged with 10^4 CFU of Staph. aureus.

The zone of inhibition determination was made following Bioassay A, described in Example 5. The Agar Lumen test was conducted as follows:

5 cc of trypticase soy agar (TSA) was solidified in a culture tube. A cork borer was used to remove a central core of agar from the tube leaving a lumen into which a 4cm section of a coated catheter having an outside dimention approximating that of the lumen opening was inserted. 1.2 cc of sterile urine was introducd into the lumen before th catheter was inserted. Once the catheter was inserted, an inoculum comprising a suspension containing $2x10^5$ CFU of a mixture of 50% Escherichia coli and 50% Staphylococcus epidermidis

was swabbed around the upper opening of the lumen adjacent the catheter.

The culture tube was incubated at 37°C. Once in each subsequent 24 hour period over the course of the test, 0.2 cc of urine was removed from within the catheter and lumen and the lumen was supplied with a fresh quantity, .2 cc, of sterile urine, which had just been inoculated with $2x10^5$ CFU of the 50% E. coli and 50% Staph. epi inoculum. At the same time, 0.01 cc of the solution removed from the lumen was tested by subculturing on a blood agar plate to determine the presence or absence of microorganisms in the liquid. In Table V below is given the number of days before growth of microorganisms was observed, either visually in the agar surrounding the lumen or in the urine samples analyzed on blood agar plates.

Comparative results between commercially coated catheters and those coated in accordance with this invention further demonstrated the significant improvement obtained; the greater the zone of inhibition, the greater the degree of suppression and cidal tendencies. Table V, below gives the results of this series of tests.

TABLE V

Antibacterial Efficacy of Urinary Catheter

Drugs in Catheter Coating	Agar Lumen Test (Days)	Zone of Inhibition (mm)	Activity in Presence of TSB (Days)
1. Silver Sulfadiazine	7 (static)	11	2
2. Silver nitrate	5 (static	9	1
3. Silver nitrate + sulfadiazine	7 (static)	11	2
4. Chlorhexidine	>15 (cidal)	20	>10
5. Silver sulfadiazine + chlorhexidine	>15 (cidal)	20	>10
6. Silver nitrate + chlorhexidine	>15 (cidal)	20	>10
7. Silver nitrate + sulfadiazine + chlorhexidine	>15 (cidal)	20	>10
8. Silver oxide (Baxter Travenol)	1 (static)	10	0
9. No drug (Control)	0	0	0

Example 3

Multicoating

At times, urinary catheters or intravenous catheters coated with biomedical polyurethane and bio-active agents or silicone (with or without PLA) and bio-active agents are found to possess surface characteristics not fully desirable. To overcome this problem, the invention further comprises the provision of a second (or more) coatings.

It has been found that a second coating applied over the biomedical polyurethane coating by spraying, dipping or otherwise, of between 0.5 and 5% of a silicone such as MDX4-4195, Dow Corning, in solution in hexane, preferably 2%, after drying, renders the coated medical device, especially a catheter, smoother in texture, with improved lubricity, without interfering with the controlled release characteristics as shown in Table VI.

TABLE VI

Retention of Antibacterial Efficacy in Presence of TSB Culture

Drug Coated Catheter Sample	Bacterial Growth Days						
	1	2	3	4	5	6	7
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	1+	2+
4	0	0	0	0	0	0	0
5	0	0	0	0	1+	2+	4+
6	0	0	0	0	0	0	1+
7	0	0	0	0	0	0	1+
8	0	0	0	0	0	0	1+
9	0	0	0	0	0	0	1+
Control Catheter No Antimicrobial Agent	Heavy (++)						

2cm segments of drug coated catheters (AgSD + CHA) in a biomedical polyurethane coating agent os 3% Pellethane® 2363-80AE in a solvent of THF + ethanol or DMAC + ethylacetate were coated with a second coating by applying thereto a 2% solution of MDX4-4195 in hexane. After thorough drying to remove solvent, the segments were suspended in 5ml TSB containing 10^4 Staph. aureus and incubated at 37°C. Every 24 hours, for seven days, the bacterial growth in the culture was measured by visual turbidity and colony counts and the catheter segment was transferred to fresh culture and the experiment repeated.

Bacterial growth was properly suppressed for seven days. In addition, the catheters possessed smoother surfaces. This multi-coating process can also use PLA in the first coating, and over a range of 0.2 to 2%, preferably 1%, in the coating vehicle with improved results.

Example 4

Coating Antimicrobial Agents and Heparin or Dextran Sulfate on I.V. Catheters

It is sometimes important that certain medical devices possess bio-activity beyond antimicrobial effects. To this end, it has been found that other bio-active agents can be incorporated into the matrices without hampering the antimicrobial aspects.

As a preferred embodiment, polyurethane catheters were coated with a biomedical polyurethane coating vehicle containing 1% chlorhexidine + 1% AgSD + 0.2% heparin. The heparin imparts anti-coagulent effects to the catheter. Likewise, dextran sulfate was incorporated in the same quantities.

Table VII, below provides data showing that the addition of heparin to the coating vehicle does not interfere with antimicrobial activity of the coated device.

TABLE VII

Retention of Antibacterial Efficacy in Heparin-Coated Catheters

	Retention of Antimicrobial Activity (Days)	
	With Heparin	Without Heparin
Triple lumen catheter	6	6
Single lumen catheter	4	4

The testing was done in TSB culture as described above. The coating which was made as follows: 0.2gm of

heparin was dissolved in 2-3cc of water to which 7ml of ethyl alcohol was added. 3gm of biomedical polyurethane, Pellethane® 2363-80AE, was dissolved in 75ml of THF and the heparin solution mixed therein. 1gm of chlorhexidine acetate was dissolved in 15 ml of ethanol, after which 1gm of AgSD was suspended therein. The antimicrobial agent solution was mixed with the polyurethane solution, and agitation maintained to insure a uniform suspension. The catheters were dipped in the solution, dried and tested. Coating can also be done in stages, i.e., a first coating of antimicrobial + matrix, followed by a second of heparin + matrix.

Example 5

Arterial grafts of two commercially available types were provided with an antimicrobial coating in accordance with the invention. One was an expanded polytetrafluorethylene (PTFE) sold under the Gortex® name as a reinforced expanded PTFE vascular graft 8 mm in diameter. The second was a 6 mm straight woven Dacron® arterial graft sold by Bard.

Short sections of each of these materials were coated with each of the following coating vehicles:

1. 1% PLA + 1% polyurethane + 1% CHA + 3% pipracil in

25% NEP
75% THF

2. 0.5% PLA + 0.5% polyurethane + 1% CHA + 3% pipracil in

25% NEP
75% THF

100 ml batches of these coating vehicles were prepared by dissolving 3 gm of pipracil in 20 cc of NEP. 1 gm of CHA was separately dissolved in 5 cc of NEP. The required amount, either 1 gm or 0.5 of polyurethane was dissolved in 50 cc of THF and the same amounts of PLA were dissolved in 25 cc of THF. The four solutions were then combined and thoroughly mixed to provide the coating vehicles.

The polyurethane used was Pellethane® 2363-80AE. The PTFE sections, because of their unique structure, contain a number of cavities or interstices which require either vigorous agitation or the application of a vacuum to the section in the presence of coating vehicle to insure that the coating vehicle penetrates and permeates the graft. The woven graft requires only simple agitation in coating vehicle to provide a good coating. Both products are then air dried.

A good adherent coating formed on the Dacron® graft. In the case of the PTFE graft, its characteristic surface refused to retain a surface coating. However, the coating composition was retained in the interstices, and, on drying, retained a coating composition having, by weight, one part biomedical polyurethane, one part PLA, one part CHA, and three parts pipracil in the case of coating 1, and .5 parts each of PLA and polyurethane, with one part CHA and three parts pipracil for coating 2.

The activity of the processed grafts are determined by the two types of bioassays described below:

Bioassay A

- 2cm sections of graft are embedded in a 5% sheeps blood agar plate which was inoculated with $2x10^4$ CFU Staph. aureus. Activity was determined by measuring the zone of inhibition. The graft sections were transferred to newly inoculated plates daily until antibacterial activity ceased.

Bioassay B

- 1cm section of graft were soaked in 5cc of trypticase soy broth (TSB) which was inoculated with 10^4 CFU of Staph. aureus. If there was no turbidity after 24 hours incubation at 37°C, then the material was deemed to be bacteriostatic. The grafts were transferred to new TSB and inoculated daily.

Bioassay A Group	Results Zone of Inhibition (mm)			
Days	1	3	6	9
PTFE (Formula 1)	23	19	16	12
PTFE (Formula 2)	29	20	16	12
Bard (Formula 1)	29	15	12	12
Bard (Formula 2)	29	15	14	11.5
Untreated Control	0			

Bioassay B

All processed groups show activity for more than 10 days.

Untreated Control showed heavy growth and turbidity after one day.

Example 6

An expanded polytetrafluorethylene (PTFE) hernia path was impregnated with an infection-resistant material comprising silver sulfadiazine and chlorhexidine acetate in a biodegradable matrix of poly(lactic acid) using the following method.

An impregnating vehicle was prepared by mixing 0.5% chlorhexidine acetate, 0.5% silver sulfadiazine and 1% poly(lactic acid), mw 44,000, in a solvent mixture comprising 95% ethanol and THF in the proportions of 10:90. The chlorhexidine acetate and PLA are in solution in this mixture; the silver sulfadiazine is in suspension.

An expanded PTFE hernia path, 2x2 cm and having a thickness of about 0.5 cm was soaked for 5 minutes in the impregnating vehicle prepared above, with continuous stirring to maintain a uniform suspension. The patch was then removed from the suspension, air dried for about one minute and then placed in an oven at 40°C for 24 hours.

The antibacterial efficacy of the patch was evaluated, utilizing Bioassay B described in Example 5 above. Several 1 cm^2 pieces were cut and soaked in TSB and kept in water bath shakers at 37°C. The TSB is changed daily and 4 pieces were removed at different intervals and tested for zone of inhibition. The results are given in the following table:

Days of Soaking	Zone of Inhibition (mm) against Staph. aureus after 1 day
0	24
1	22
3	20
6	20

Example 7

Method of in situ Incorporation of Silver Sulfadiazine and Chlorhexidine in Hernia Patch

The interstices of a hernia patch, which is made up of expanded PTFE, are too small for a sufficient amount of silver sulfadiazine (AgSD) molecules to enter. Therefore, silver sulfadiazine is precipitated in situ by treating the patch with sodium sulfadiazine (NaSD) and silver nitrate. The following methods were used to incorporate silver sulfadiazine and chlorhexidine acetate (CHA) into the interstices of a patch.

1. An expanded polytetrafluorethylene (PTFE) hernia patch, 2x2 cm and having a thickness of about 0.5 cm is first soaked in:

   (a) a 95% ethanol solution of 0.5% silver sulfadiazine and 0.5% chlorhexidine acetate for 2-3 minutes, removed, dried for about one minute;

   (b) the patch is then soaked in 0.25% $AgNO_3$ solution for 2-3 minutes, removed and air dried. The patch is then placed in an oven at 40°C for 24 hours.

2. The procedure is the same as in 1, but the first solution contains 0.4% sodium sulfadiazine, 0.5% chlorhexidine acetate, and 1% PLA, mw 44,000, in a solvent comprising a 95% ethanol:THF mixture (10:90). In an alternative to both the 1 and 2 methods, the first dipping step was done in $AgNO_3$ solution

and then in the mixture of sodium sulfadiazine and chlorhexidine acetate.

Evaluation of Antibacterial Efficacy of Patches Coated by this Process

Following the bioassay method of Example 6, several 1 cm^2 pieces were cut and soaked in TSB and kept in water bath shakers. The TSB was changed daily and 4 pieces were removed at different intervals and tested for zone of inhibition.

Coating Procedure	Zone of Inhibition (Days)		
	1	3	6
Method A			
NaSD + CHA → $AgNO_3$	23	21	20
$AgNO_3$ → NaSD + CHA	22	21	20
Method B			
NaSD + CHA + PLA → $AgNO_3$	22	20	19
$AgNO_3$ → NaSD + CHA + PLA	22	20	19

Example 8

A coating vehicle for use in accordance with the present invention was prepared as follows:

1 gm of chlorhexidine acetate (CHA) was added to 5 cc of N-ethyl-2-pyrrolidone (NEP). The mixture was heated to 50-60°C and agitated in a Vortex® stirrer until the CHA dissolved.

10 cc tetrahydrofuran (THF) was then added to the CHA solution in NEP and the mixture thoroughly agitated to form a uniform solution.

3 gm of Pellethane® 2363-80AE of the Dow Chemical Co. was added to 50 cc of THF. The mixture was warmed to about the boiling point of THF, 65-70° C, and stirring with a Vortex® stirrer was continued until the polyurethane was dissolved.

1 gm of silver sulfadiazine (AgSD) micronized powder was suspended in 35 cc of THF and vigorously agitated in a Vortex® stirrer to form a uniform suspension. The CHA solution in NEP and THF prepared above was then combined with the polyurethane solution and agitated to form a clear solution. As a last step in preparing the coating vehicle, the AgSD suspension in THF was added and the entire mixture agitated to maintain a uniform suspension. Thus was provided a coating vehicle containing 1% CHA and 1% AgSD as antimicrobial agents, together with 3% of the biomedical polyurethane. The solvent in this case was a mixture of solvents comprising 5% NEP and 95% THF. The CHA was in solution in the coating vehicle, while the AgSD was in uniform suspension.

The coating vehicle prepared above was used to coat an I.V. catheter fabricated of Pellethane® 2363-90A. The catheter was dipped in the coating vehicle while the vehicle was being continuously agitated to insure a uniform suspension. The coated catheter was then dried. A tightly adherent coating on the catheter was thus provided.

Example 9

Synergism of Silver Sulfadiazine (AgSD) and Chlorhexidine (CHA)

The results of experiments described below indicate that coating silver salts, preferably sulfadiazine, and chlorhexidine or its salts onto medical devices imparts prolonged antibacterial activity. In addition, in vitro studies show that chlorhexidine exhibits a synergistic effect when combined with silver sulfadiazine and thus increases the antimicrobial spectrum. AgSD + CHA also kills 99.9% of the bacterial population faster than

chlorhexidine alone which is important for its use in medical gloves and condoms. Furthermore, when wound dressings (Epilock® dressings) coated with silver sulfadiazine and chlorhexidine were tested for zone of inhibition against a mixed culture of Staph. aureus and Ps. areuginosa, a synergistic effect was observed.

Analytical Procedures for Determinating the Drug Content and Rate of Release from Devices

Determination of silver (Ag), sulfadiazine (SD) and chlorhexidine acetate (CHA) values is performed as follows:

Silver and SD

The devices (catheters) were coated with radioactive silver sulfadiazine (^{110}AgSD) and after measuring the initial radioactivity they were suspended in culture media or saline. The catheters were transferred daily to fresh media or saline and the radioactivity remaining in the catheter segments were measured using a Nuclear Chicago 1185 automated gamma counter. The amount of SD released was measured by determining the SD content of the media using a calorimetric method (Bratton-Marshal Test).

Initial levels of SD in the catheters were determined by extracting the SD from the catheters with 0.2 molar nitric acid.

CHA

CHA levels are determined spectrophotometrically (231nm and 254nm) using a Hitachi® 2000 double beam UV/VIS system. Initial levels were measured by extracting the CHA from the catheter using warm ethanol. The CHA released into the media was also measured spectrophotometrically. These spectrophotometric levels wer corroborated by bioassay such as zone of inhibition tests.

In vitro Studies

Different concentrations of silver sulfadiazine or chlorhexidine alone or in combinations were added to mixed cultures of Ps. areuginosa and Staph. aureus (10^5 CFU each organism) in 2 ml trypticase soy broth (TSB) and incubated along with control cultures. 0.1 ml aliquots were removed from these cultures and diluted to 10 ml (1 to 100 dilution) at 10 minutes, 20 minutes and 40 minutes. 0.2 ml of these diluted samples were subcultured on blood agar plates and colony counts were made 24 hours post incubation. The results are given the following Table VIII.

TABLE VIII

Bacterial Inhibition

Antimicrobial Agent	Concentration (µmole/2 ml)	Colony Forming Units (CFU)		
		10 minute	20 minute	40 minute
None	0	$>10^6$ (S&P)	$>10^6$ (S&P)	$>10^6$ (S&P)
AgSD	1.0	$2x10^5$ (S&P)	$1x1x10^5$ (S&P)	$1.2x10^5$ (S&P)
CHA	1.0	$1x10^3$ (S)	0	0
AgSD + CHA	1.0 + 1.0	0	0	0
AgSD	0.5	$>10^6$ (S&P)	$>10^6$ (S&P)	$>10^6$ (S&P)

CHA	0.5	$1x10^5$ (S)	$3.7x10^4$ (S)	$2x10^2$ (S)
AgSD + CHA	0.5 + 0.5	0	0	0

S&P = Staph. aureus and Ps. aeruginosa
S = Staph. aureus

The results show:

1. chlorhexidine acts rapidly, and by 20 minutes kills the organisms present;
2. silver sulfadiazine exhibits steady and prolonged suppression of growth (also see the example relating to wound dressings below); and
3. AgSD + CHA demonstrate a marked improvement over the individual results as there is even a more rapid kill (10 minutes), and prolonged suppression.

The results clearly show a fast and prolonged and synergistic antibacterial activity for the combination of AgSD + CHA, exhibiting far superior results than by using each such antimicrobial agent alone.

Example 10

Synergistic results are also found when other silver salts are combined with chlorhexidine, as shown in Table IX; below.

TABLE IX

Synergistic Effect of Silver Compounds and Chlorhexidine against Staph. aureus, in vitro

Drug Concentration in Culture	Colony Count (Minutes)	
	20	60
100µg silver sulfadiazine	9,500	8,000
100µg silver oxide	7,500	8,000
100µg silver carbonate	9,200	6,000
100µg chlorhexidine acetate	6,250	4,000
50µg silver sulfadiazine + 50µg chlorhexidine acetate	4,800	0
50µg silver oxide + 50µg chlorhexidine acetate	3,700	0
50µg silver carbonate + 50µg chlorhexidine acetate	4,300	0
100µg silver nitrate	10,500	11,000
100µg chlorhexidine, water insoluble	6,000	3,000
50µg silver nitrate + 50µg chlorhexidine, water insoluble	100	0
CONTROL	16,000	15,000

For Table IX, 3 ml of TSB culture of Staph. aureus (10^4 CFU/ml) containing the drug were incubated for one hour at 37°C and the colony counts measured. The results achieved further show the synergistic interaction between silver salts and chlorhexidine salts in causing complete suppression of growth by 60 minutes, whereas each anti-bacterial agent, alone, showed only partial suppression.

Example 11

Methods for the Preparation of Coated Medical Devices and Evaluation of Antibacterial Activity

Certain medical devices are comprised of materials not fully compatible with biomedical polyurethane as a coating vehicle, requiring, for compatible matrices, the use of a biomedical silicone, with or without a biodegradable polymer such as poly(lactic acid) (PLA).

Method A

Chlorhexidine diacetate is mixed uniformly in 1% to 10%, preferably 5%, silicone solution in ethyl acetate, or silicone solution containing .2 to 2%, preferably 0.5% or 1% poly(lactic acid), molecular weight 2000. The medical device is dipped for 10 seconds in this suspension which is kept at room temperature. The silicone used was Silastic® Medical Adhesive Silicon Type A.

Method B

0.5 to 10% chlorhexidine diacetate is mixed uniformly in 1% PLA solution (equal amounts of 2,000, 44,000, 100,000 and 300,000 molecular weight PLA) in ethyl acetate. This antimicrobial suspension is kept at 50°C in a water bath and mixed continuously. The medical device to be coated is dipped for one minute in this suspension, removed and dried.

In both of the above methods, other antimicrobial agents can also be used either singly or in combination as shown below.

Coating of Latex Gloves

The fingers of latex medical gloves were washed, dried and dip-coated with (a) chlorhexidine acetate (CHA), (b) CHA and silver sulfadiazine (AgSD), and (c) AgSD using antimicrobial suspensions prepared by Method A above. The silicone used in this test was a mixture of equal parts by weight of Silastic® Medical Adhesive Silicone Type A, and MX-4-4159, a fluid comprising equal parts of an active polydimethyl siloxane and a solvent therefor comprising mixed aliphatic and isopropanol solvents. The PLA employed was a poly(L-lactic acid) procured from Polysciences, Inc., Warington, Pennsylvania, having various molecular weights. PLA-2000 has a molecular weight of 2000. The suspension had the following composition:

1. 10% CHA + 10% silicone + 0.5% PLA-2000
2. 5% CHA + 5% AgSD + 10% silicone + 0.5% PLA-2000
3. 10% silver sulfadiazine + 10% silicone + 0.5% PLA-2000

The antibacterial efficacy was tested against a mixed culture of Pseudomonas aeruginosa and Staphylococcus aureus having 10^4 CFU of each per 2 ml of culture.

The coated fingers were suspended in culture tubes and 2 ml of 5% bovine albumin solution containing the mixed bacterial culture were added to it and incubated at 37°C. The rate of killing was determined by taking aliquots at 10, 20 and 40 minutes and subculturing on blood agar plates for colony counts. The results are given in Table X below.

TABLE X

Colony Counts of Staph. aureus and Ps. aeruginosa (Colony Forming Units - CFU/2 ml Culture)

Antimicrobial Agent on Gloves	10 Minutes		20 Minutes		40 Minutes	
	Staph. aureus	Ps. aer.	Staph. aureus	Ps. aer.	Staph. aureus	Ps. aer.
CHA	$8x10^3$	0	$2x10^3$	0	0	0
CHA + AgSD	$4x10^3$	0	0	0	0	0
AgSD $5x10^3$	$1x10^4$	$1.2x10^4$	$5x10^3$	$8x10^3$	$4x10^3$	
None (Control) $2x10^4$ $8x10^3$		$1x10^4$	$1x10^4$	$1x10^4$	$8x10^3$	

These results demonstrate improved and sustained suppression of bacterial growth when using the combination of CHA + AgSD on gloves.

Example 12

Coating of Urinary Catheters and Evaluation of Antibacterial Activity

Using the methods described in A and B in Example 11 above, latex urinary catheters were coated with a coating vehicle containing Silastic® Medical Adhesive Silicone Type A in Method A and PLA in Method B, both having various amounts of chlorhexidine and/or silver sulfadiazine and 2.0 cm segments were soaked in either 5 ml trypticase soy broth (TSB or 5 ml urine inoculated with a mixture of 10^4 organisms of Staph. epi and E. coli. After 24 hours of incubation at 37°C, the media was subcultured to quantitatively determine bacterial levels. The segments were then transferred to fresh media which was re-inoculated. This procedure was continued until the urinary catheter segments no longer presented antibacterial activity. The results, showing significant retention of bio-active material are given in Table XI below.

TABLE XI

Retention of Antibacterial Activity of Coated Urinary Catheters

Antimicrobial Agent on Urinary Catheters	Retention (Days)			
	% Anti-Microbial in coating Solution	In Presence of Urine	In Presence of TSB	Nutrient Agar Plate
Method A - CHA	10	5	4	>7
Method A - CHA	5	4	3	5
Method A - AgSD	5	2	2	5
Method A - CHA + AgSD	5+5	3	3	>7
Method A - None (Control)	0	0	0	0
Method B - CHA	10	6	4	>7
Method B - CHA	5	4	3	5
Method B - AgSD	4	2	2	5
Method B - CHA + AgSD	5+5	3	3	6
Method B - None (Control)	0	0	0	0

CHA = chlorhexidine acetate

AgSD = silver sulfadiazine

Example 13

Antibacterial Efficacy of Coatings Containing Chlorhexidine Acetate and Biodegradable Polymers on Polyurethane I.V. Catheters

Using the method described as Method B in Example 11 above, I.V. catheters fabricated of Pellethane® 2363-80AE, a biomedical polyurethane, were coated with a coating vehicle which, in a first series, contained 1% chlorhexidine acetate in a solvent comprising 10% of 95% ethanol and 90% ethyl acetate. A second series used a coating vehicle containing 1% chlorhexidine acetate and 3% of Pellethane® 2363-80AE in a solvent comprising 10% of 95% ethanol and 90% of THF. The third series used a coating vehicle comprising 1% chlorhexidine acetate, 5% of Silastic® Type A Medical Adhesive, a polymethyl siloxane, and 2% of MDX 4-4159, a silicone comprising 50% of an amino functional polydimethyl siloxane copolymer and 50% mixed aliphatic and isopropanol solvents. In addition, each of the three series contained a biodegradable polymer at a level of 1%; the polymers were obtained from Polyscience.

The procedure described in Example 12 was used to test 2.0 cm segments of the coated catheter. The results obtained are summarized in the following table:

Biodegradable Polymers	1-day Zone of Inhibition (mm)		
	CHA Alone	CHA with Polyurethane	CHA with Silicone
Poly(lactic acid), mw 100,000	21	21	20
Polycaprolactone	20	19	19
Polyhydroxybutyric acid, mw 30,000	20	21	21

The zone of inhibition was tested on blood agar culture plates seeded with Staph. aureus (10^4 organisms).

Example 14

Multicoating

At times, urinary catheters or intravenous catheters coated with biomedical polyurethane and bio-active agents or silicone (with or without PLA) and bio-active agents are found to possess surface characteristics not fully desirable. To overcome this problem, the invention further comprises the provision of a second (or more) coatings.

It has been found that a second coating applied over the biomedical polyurethane coating by spraying, dipping or otherwise, of between 0.5 to 5% of a silicone fluid such as the MDX4-4159 described in Example 11 in solution in hexane, preferably 2%, after drying, renders the coated medical device, especially a catheter, smoother in texture, with improved lubricity and improved retention characteristics, as shown in Table XII.

TABLE XII

Retention of Antibacterial Efficacy in Presence of TSB Culture

Drug Coated Catheter Sample	Bacterial Growth Days						
	1	2	3	4	5	6	7
MDX Coating							
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	1+	2+
4	0	0	0	0	0	0	0
5	0	0	0	0	1+	2+	4+
6	0	0	0	0	0	0	1+
7	0	0	0	0	0	0	1+
8	0	0	0	0	0	0	1+
9	0	0	0	0	0	0	1+
No MDX Coating							
1	0	0	0	0	0	1+	
2	0	0	0	0	1+	1+	
3	0	0	0	0	1+	1+	
4	0	0	0	0	1+	1+	
5	0	0	0	0	1+	1+	
6	0	0	0	0	0	1+	
Control Catheter No Antimicrobial Agent	Heavy (++)						

2 cm segments of drug coated catheters (AgSD + CHA) in a biomedical polyurethane coating agent of 3% Pellethane® 2363-80AE in a solvent of THF + ethanol or DMAC + ethylacetate were coated with a second coating by applying hereto a 2% solution of MDX4-4159 in hexane. After thorough drying to remove solvent, the segments were suspended in 5 ml TSB containing 10^4 Staph. aureus and incubated at 37°C. Every 24 hours, for seven days, the bacterial growth in the culture was measured by visual turbidity and colony counts and the catheter segment was transferred to fresh culture and the experiment repeated.

Bacterial growth was properly suppressed for seven days. In addition, the catheters possessed smoother surfaces. This multicoating process can also use PLA in the first coating, and over a range of 0.2 to 2%, preferably 1%, in the coating vehicle with improved results.

Example 15

Coating Antimicrobial Agents and Heparin or Dextran Sulfate on I.V. Catheters

It is sometimes important that certain medical devices possess bio-activity beyond antimicrobial effects. To this end, it has been found that other bio-active agents can be incorporated into the matrices without hampering the antimicrobial aspects.

As a preferred embodiment, polyurethane catheters were coated with a biomedical polyurethane coating vehicle containing 1% chlorhexidine + 1% AgSD + 0.2% heparin. The heparin imparts anti-coagulent effects to the catheter. Likewise, dextran sulfate was incorporated in the same quantities.

Table XIII, below provides data showing that the addition of heparin to the coating vehicle does not interfere with antimicrobial activity of the coated device.

TABLE XIII

Retention of Antibacterial Efficacy in Heparin-Coated Catheters

	Retention of Antimicrobial Activity (Days)	
	With Heparin	Without Heparin
Triple lumen catheter	6	6
Single lumen catheter	4	4

The testing was done in TSB culture as described above. The coating which was made as follows: 0.2 gm of heparin was dissolved in 2-3 cc of water to which 7 ml of ethyl alcohol was added. 3 gm of biomedical polyurethane, Pellethane® 2363-80AE, was dissolved in 75 ml of THF and the heparin solution mixed therein. 1 gm of chlorhexidine acetate was dissolved in 15 ml of ethanol, after which 1 gm of AgSD was suspended therein. The antimicrobial agent solution was mixed with the polyurethane solution, and agitation maintained to insure a uniform suspension. The catheters were dipped in the solution, dried and tested. Coating can also be done in stages, i.e., a first coating of antimicrobial + matrix, followed by a second of heparin + matrix.

Example 16

Coating of Wound Dressings

Johnson and Johnson gauze dressings and Epilock® dressings manufactured by Dermalock Medical Corporation were coated with antimicrobial agents. These coated dressings were prepared using methods (a) and (b) above. The zone of inhibition was tested against a mixture of Ps. aeruginosa and Staph. aureus cultures on nutrient agar plate.

TABLE XIV-A

Antibacterial Activity of Johnson and Johnson Dressings

Antimicrobial Agent in Dressings	% Antimicrobial Agent in Coating Solution	Zone of Inhibition (mm)	
		1 day	2 day
Method A - CHA	10	27	20
Method A - AgSD	5	25	18
Method A - CHA + AgSD	5+5	25	20
None (Control)	0	0	0

TABLE XIV-B

Antibacterial Activity of Epilock® Dressings

Antimicrobial Agent in Dressings	% Antimicrobial Agent in Coating Solution	Zone of Inhibition (mm)				
		1	2	3	4	5 Days
Method A - CHA	10	28	28	43	40	25
Method A - AgSD	5	30	35	43	27	28
Method A - CHA + AgSD	5+5	34	45	43	27	34
Method B - CHA	10	27	21	22	24	24
Method B - AgSD	5	31	35	35	0	0
Method B - CHA + AgSD	5+5	38	28	37	30	25
None (Control)	0	0	0	0	0	0

These results demonstrate the improvement in using the synergistic combination, as well as the general efficacy of the process. Wound dressings may also be provided with an adhesive on one side (to attach to the wound). In such cases, the invention further comprises seven methods of application of the antimicrobial agent:

1. Suspending the antimicrobial agents, preferably silver sulfadiazine and chlorhexidine in the quantities of 1-5% total, in a carrier that evaporates but does not solubilize the adhesive, instead leaving the adhesive intact, e.g., an alcohol, and spraying the agent-containing carrier upon the dressing, or dipping the dressing into the agent-containing carrier solution.
2. Placing the antimicrobial agents in a solution containing silicone or polyurethane (preferably 1%) and a carrier (preferably ethyl acetate, THF or H_2O and spraying it upon the dressing, or dipping the dressing into it.
3. Applying powdered antimicrobial agents (preferably silver sulfadiazine and chlorhexidine) to the adhesive in microlayers that do not eliminate adhesion.
4. Admixing powdered antimicrobial agents with adhesive prior to application.
5. Adding a biodegradable material containing antimicrobial agents to the adhesive to provide controlled-release through degradation.
6. Providing spots containing antimicrobial agents, surrounded by adhesive.
7. Providing a biodegradable or nonbiodegradable adhesive composition containing antimicrobial agents.

Example 17

Method of Coating Antimicrobial Agents on the Surface of Latex Gloves During Automated Manufacturing Process

The invention is especially useful in the automated manufacturing of gloves. There are two methods found useful in the coating of the combination of chlorhexidine and silver sulfadiazine.

Method 1

Latex gloves are typically manufactured by (1) dipping a form in molten latex, (2) removing the latex form and transferring it to a dryer, (3) removing the form with attached glove from the dryer and immediately spraying it with a dusting powder, as it cools. A suspension of silver sulfadiazine in alcohol or water in an aqueous silicone latex emulsion (1-5% by volume) + chlorhexidine (1-5% + dusting powder (2-10%) is sprayed on the gloves as the gloves are dispenesed from the dryer at 120°C. At this temperature, the antimicrobial agents and the

dusting powder particles adhere well to the soft and/or semi-molten surfaces of the gloves. The antimicrobial activity is not in any way altered as a consequence of this process, because of the falling temperature of the gloves, as they cool. This is a preferred procedure in cases where presence of other organic solvents in the coating process is a concern to the manufacturer.

Method 2

Sterile corn starch-based dusting powder is admixed with silver sulfadiazine (1-5% by weight) and chlorhexidine (1-5% by weight) in powdered form, and the mixture is sprayed on the gloves as they are dispensed from the dryer at 120° C, and start to cool. The dusting powder with enhanced antimicrobial activity remains with the gloves.

Example 18

Preparation of Infection-Resistant Devices with Silver Sulfadiazine and Chlorhexidine Using a Mixture of Silicones as the Polymeric Coating Agent

In order to obtain a coating which is lubricious, adheres well to the catheter and also releases the drug in a controlled dosing manner, a mixture of Silastic® Medical Adhesive Type A, a polydimethyl siloxane, and MDX-4-4159, a fluid silicone comprising equal parts of an amino functional Polydimethyl siloxane copolymer and a mixed aliphatic and isopropanol solvent were used as the polymericcoating agents. Silastic® Medical Adhesive Silicone Type A alone forms an undesirable surface, while the MDX-4-4159 alone does not form an adherent film on the surface. However, use of a mixture of these two silicones in 1:1 proportions gives a coating vehicle which forms a film with the desired biocompatible characteristics. The Silastic® functions as the bonding agent whereas the MDX-4-4159 imparts lubricity to the surface. In addition, the MDX-4-4159 prolongs the release of the antimicrobial agent.

The coating agent was prepared by dispersing 2.5ml of Silastic® Medical Adhesive Type A in 55ml of THF to which 2.5 ml of MDX-4-4159 is added. 4 g of Ag SD are suspended in 30ml and 2g of CHA are dissolved in 10ml of ethanol. The AgSD suspension is mixed with the silicone dispersons and finally the CHA solution is added dropwise while the preparation is agitated. Either 5% NEP or 5% DMAC can be substituted for ethanol in the above formulation.

The coating agent prepared above was used to apply a coating on catheters fabricated from silicone, polyurethane and latex substrates. The coatings were applied by dipping and drying, as described in Example 2. Results are given in Table XV below.

TABLE XV

Antibacterial Efficacy of Polyurethane I.V. Catheters and Latex or Silicone Urinary Catheters Coated with A silicone Matrix

Catheter Type	Drug in Catheter	Days of Activity*
Polyurethane I.V.	CHA	2
Polyurethane I.V.	AgSD + CHA	4
Latex urinary	AgSD	2
Latex urinary	AgSD + CHA	4
Silicone urinary	AgSD	3
Silicone urinary	AgSD + CHA	4

* Determined via Bioassay A. Inoculum used to assay urinary catheter is a 10^4 CFU of a 1:1 mixture of Staph. epi and E. coli; 10^4 CFU of Staph. aureus is used to challenge the I.V. catheter.

Example 19

Silver sulfadiazine and chlorhexidine acetate were added over a range of proportions to cultures of Staph.

aureus containing 10^5 colony forming units (CFU) in 2 ml trypticase soy broth (TSB) and the cultures were incubated along with control cultures at 37°C. 0.1 ml aliquots were removed from these cultures and diluted to 10 ml, a 1:100 dilution after one hour. 0.2 ml of these diluted samples were subcultured on blood agar plates and colony counts were made 24 hours post incubation. The results are given in the following Table XVI.

TABLE XVI

Synergism of Different Combinations of Silver Sulfadiazine (AgSD) and Chlorhexidine (CHA) against Staph. aureus

Concentration µg/2 ml AgSD + CHA		Bacterial Inhibition Colony Forming Units After 1 Hour
0	100µg	650
25µg	75µg	100
50µg	50µg	150
75µg	25µg	100
87.5µg	12.5µg	150
100µg	0	3,100
0	0	4,100

Example 20

Coating of Latex Gloves

The fingers of latex gloves were washed and dried. They were then sprayed with a fine mist spray of a coating solution to provide a uniform coating of solution on the glove surface, sufficient to provide complete wetting thereof without runoff. The coating solutions were prepared by dissolving 1% Silastic® Medical Adhesive Type A and 1% of the silicone MDX4-4159 in ethyl acetate, followed by dissolving and dispersing the chlorhexidine acetate and silver sulfadiazine, respectively, therein. The coating was air dried for 24 hours and the gloves tested using the following test:

Treated glove fingers were draped over the tops of culture tubes with the treated side with sprayed on coating forming the inside on the cup shape. Then 3.0 ml of TSB containing 10^4 colony forming units of Staph. aureus was dispensed in each finger and all placed in a water bath shaker at 37°C. Samples were removed at 15 minutes, 1 hour, 2 hours, and 4 hours, diluted 1-10, and the solution placed on blood agar in 2.0 ml amounts.

The results of the test are summarized in the following Table XVII.

TABLE XVII

Antibacterial Efficacy of Drug Coated Gloves against Staph. aureus

Drug in Coating Solution	15 minutes	Colony Counts 8 hours	24 hours	48 hours
None (Control)	12,000	15,000	20,000	50,000
Chlorhexidine (1%)	100	0	0	0
Silver Sulfadiazine (2%)	3,300	200	0	0
Silver Sulfadiazine (1%) + Chlorhexidine (1%)	0	0	0	0

It is noted that the gloves coated according to this procedure were flexible and met all other requirements for high quality latex gloves.

Example 21

The fingers of latex gloves were washed, dried, and sprayed with a fine mist of a coating solution to provide a uniform coating of solution on the glove surface, sufficient to provide a complete wetting thereof without runoff. The coating solutions were prepared by dissolving 1% Silastic® Medical Adhesive Type A and 1% of the silicone MDX4-4159 in ethyl acetate, followed by dissolving or dispersing the chlorhexidine acetate and silver sulfadiazine respectively therein. The coating was air dried for 24 hours and the gloves tested using the following test:

Treated glove fingers were draped over the tops of culture tubes with the treated side with sprayed on coating forming the inside on the cup shape. Then 3.0 ml of TSB containing 10^3 colony forming units of Candida albicans was dispensed in each finger and all placed in a water bath shaker at 37° C. Samples were removed at 15 minutes, 1 hour, 2 hours, and 4 hours. They were diluted 1-10 and plated on blood agar in 2.0 ml amounts.

The results of the test are summarized in the following Table XVIII.

TABLE XVIII

Antibacterial Efficacy of Drug Coated Gloves against Candida albicans

Drug in Coating Solution	Colony Counts in Culture			
	15 min.	1 hour	2 hours	4 hours
None (Control)	1,400	2,000	4,000	6,000
Chlorhexidine (1%)	75	0	0	0
Silver sulfadiazine (2%)	1,650	1,500	1,500	2,200
Silver sulfadiazine (1%) + Chlorhexidine (1%)	0	0	0	0

As in Example 20, the gloves coated according to this procedure were flexible and met all requirements for high quality latex gloves.

Example 22

The fingers of latex gloves were washed and dried. They were then sprayed with a fine mist spray of the

coating solution in runs 1-3 below to provide a uniform coating of solution on the glove surface, sufficient to provide a complete wetting without runoff, after which the gloves were dried for 24 hours. In run 4, the powder was blown on to the gloves to form a uniform coating.

The coating solutions were prepared having the following ingredients:

1. 1% MDX4-4159 + 1% Silastic® Medical Adhesive Type A + 1% CHA + 1% AgSD + 2% starch-based dusting powder in ethyl acetate.
2. 1% CHA + 1% AgSD + 2% dusting powder in ethanol.
3. 1% chlorhexidiene gluconate (CHG) + 1% AgSD + 2% dusting powder in ethanol.
4. A mixture of CHA + AgSD + dusting powder in equal weight ratios.

The coated gloves were tested, following the procedure set forth in Example 16 above. The results are given in Table XIX.

TABLE XIX

Antibacterial Efficacy of Drug Coated Gloves against Staph. aureus

Coating Solution	Colony Counts in Culture	
	15 min.	1 hour
1	0	0
2	0	0
3	0	0
4	0	0
None (Control)	12,000	15,000

It is noted that other medical gloves, including surgical and examination gloves, fabricated from other materials such as polyurethane, polyethylene, polypropylene, and polyvinyl acetate, may be coated following the process of this invention.

It is further noted that in both the dry powder process and the so-called wet powder process using a vehicle such as ethanol, the antimicrobial powders and dusting powders may be applied separately, and in any sequence.

Example 23

This example illustrates the coating of medical gloves with a coating composition containing an aqueous silicone emulsion.

15 grams of starch-based dusting powder is suspended in 50 ml of deionized water. The suspension is then mixed with 44.5 ml of deionized water in which 2 grams of micronized silver sulfadiazine is suspended. To this mixture is added .5 cc of L.E. 46, a silicone emulsion containing 35% dimethyl siloxane, sold by Dow Corning Company. Finally, 5 cc of a 20% chlorhexidine gluconate in water is added and the mixture stirred to maintain a uniform suspension.

Washed latex glove fingers are dipped into the mixture and air dried for one minute to provide an adherent, infection-resistant, coating.

Example 24

Latex urinary catheters were provided with coatings including a series of antimicrobial agents. A coating solution was prepared containing 6% Dow Pellethane® 80AE in solvent comprising 5% NEP and 95% THF. The catheters were dipped in the solution to provide a uniform coating, and dried for 24 hours to remove the solvent. When used alone, the Ag salt was used at a 5% level. When a combination of agents were used, the silver salt was at a 2% level, as was the CHA. All silver salts were very finely divided, either by grinding in a mortar and pestle, or by purchase of micronized grade materials. Three 1 cm segments of each catheter were placed in the center of blood agar plates seeded with 10^4 CFU of a 1:1 mixture of Staph. epi and E. coli, one section to each plate, and the zone of inhibition was measured after incubation at 37°C for 24 hours. The results are given in the following Table XX.

TABLE XX

Antibacterial Efficacy of Drug Coated Urinary Catheters against Staph. epi and E. coli

Drug on Catheter	Zone of Inhibition (mm), Days					
	Days 1	2	3	4	5	6
Chlorhexidine (CHA)	18	23	15	16	15	14
Silver acetate	12	13	12	12	12	11
Silver acetate + CHA	20	21	14	14	12	12
Silver benzoate	13	12	10	11	11	12
Silver benzoate + CHA	18	20	12	13	13	14
Silver carbonate	13	12	12	12	12	13
Silver carbonate + CHA	20	23	19	12	13	13
Silver iodate	10	0	0	0	0	0
Silver iodate + CHA	18	20	15	14	14	15
Silver laurate + CHA	22	24	19	18	18	17
Silver protein	10	0	0	0	0	0
Silver protein + CHA	26	26	15	16	16	17
Silver palmitate + CHA	26	26	23	18	18	18
Silver chloride	11	6	6	10	10	10
Silver chloride + CHA	20	15	14	15	15	15
Silver oxide	14	12	11	12	12	12
Silver oxide + CHA	22	25	15	14	15	15
Silver sulfadiazine	8	8	7	10	10	10
Silver sulfadiazine + CHA	20	15	15	15	16	16
Silver tannate + CHA	20	-*	-	-	-	-

* Experiment discontinued after 1 day because of poor quality coating.

Example 25

I.V. catheters fabricated of Pellethane® 2363-90A were provided with coatings including a series of antimicrobial agents. A coating solution was prepared containing 6% Dow Pellethane® 2363-80AE and the drug in a solvent comprising 5% N-ethyl-2-pyrrolidone (NEP) and 95% tetrahydrofuran (THF). When used alone, the Ag salt was used at a level of 5%. When combined with CHA, each was used at a level of 2%. The catheters were dipped in the solution to provide a uniform coating on the device, and thereafter allowed to dry for 24 hours to remove the solvent.

Three 1 cm segments of each catheter were placed in the center of blood agar plates seeded with 10^4 CFU of Staph. aureus, one section to a plate, and the zone of inhibition was measured after 24 hours at 37°C.

Results, expressed as the average of 3 determinations, are given in the following Table XXI.

TABLE XXI

Antibacterial Efficacy of Drug Coated I.V. Catheters against Staph. aureus

Drug on Catheter	Zone of Inhibition (mm),				
	1	2	3	4	5
Chlorhexidine (CHA)	15	12	12	9	9
Silver acetate	10	8	10	9	8
Silver acetate + CHA	18	11	11	14	11
Silver benzoate	12	8	11	10	12
Silver benzoate + CHA	18	11	25	13	13
Silver carbonate	11	7	10	10	10
Silver carbonate + CHA	17	12	17	13	13
Silver iodate	7	0	0	0	0
Silver iodate + CHA	18	12	17	12	8
Silver laurate + CHA	25	13	21	15	12
Silver protein	10	0	0	0	0
Silver protein + CHA	19	11	12	12	9
Silver chloride	9	5	6	3	3
Silver chloride + CHA	18	11	17	13	13
Silver oxide	11	7	10	9	9
Silver oxide + CHA	20	10	13	12	14
Silver sulfadiazine	13	5	8	9	7
Silver sulfadiazine + CHA	16	11	15	14	13
Silver tannate + CHA	19	-	-	-	-*

* Experiment discontinued after 1 day because of poor quality coating.

Example 26

I.V. catheters fabricated of Pellethane® 2363-90A were provided with coatings including a series of antimicrobial agents. A coating solution was prepared containing 6% Dow Pellethane® 2363-80AE and the drug in a solvent comprising 5% N-ethyl-2-pyrrolidone (NEP) and 95% tetrahydrofuran (THF). When used alone, the Ag salt was used at a level of 5%. When combined with CHA, each was used at a level of 2%. The catheters were dipped in the solution to provide a uniform coating on the device and thereafter allowed to dry for 24 hours to remove the solvent.

1 cm segments of each catheter were soaked in TSB and incubated at 37°C in a water bath shaker. At intervals of 0, 3, 9, and 12 days, 3 segments were recovered from each group, placed in the center of blood agar plates seeded with 10^4 CFU of Staph. aureus, one section to a plate, and the zone of inhibition was measured after 24 hours at 37°C. Results, expressed as an average of 3 determinations, are given in the following Table XXII.

TABLE XXII

Antibacterial Efficacy of Drug Coated I.V. Catheters against Staph. aureus in Presence of Trypticase Soy Broth

Drug on Catheter	Zone of Inhibition (mm), Days			
	3	6	9	12
Chlorhexidine (CHA)	14	12	12	11
Silver acetate	9	9	9	9
Silver acetate + CHA	15	11	12	10
Silver benzoate	10	10	10	10
Silver benzoate + CHA	13	10	12	12
Silver carbonate	10	10	12	10
Silver carbonate + CHA	14	13	13	12
Silver iodate	2	0	0	0
Silver iodate + CHA	15	15	10	10
Silver laurate + CHA	26	15	15	15
Silver protein	8	0	0	0
Silver protein + CHA	15	12	15	15
Silver palmitate + CHA	26	15	15	17
Silver chloride	5	6	6	6
Silver chloride + CHA	20	13	13	14
Silver oxide	9	9	9	9
Silver oxide + CHA	13	13	12	12
Silver sulfadiazine	9	9	9	9
Silver sulfadiazine + CHA	19	14	12	12
Cuprous oxide	4	0	0	0
Cuprous oxide + CHA	17	13	12	12

Example 27

I.V. catheters fabricated of Pellethane® 2363-90A were provided with coatings incorporating a series of antimicrobial agents. A coating solution was prepared containing 3% Dow Pellethane® 2363-80AE and the drug in a solvent comprising 5% N-ethyl-2-pyrrolidone (NEP) and 95% tetrahydrofuran (THF). The AgSD was micronized; the Ag carbonate was ground thoroughly in mortar and pestle to very fine particle size. The catheters were dipped in the solution to provide a uniform coating on the device and thereafter allowed to dry to remove the solvent.

1 cm segments of each catheter were treated and tested according to the procedure set forth in Example 26. The results obtained, expressed as maximum period of retention of activity, are given in Table XXIII below.

TABLE XXIII

Retention of Antibacterial Efficacy of Different Drug Coated Catheters (Polyurethane I.V.) in TSB Culture (10^4 Staph. aureus)

Drugs in Coating Solution	Days of Activity Retained
None	0
AgSD (5%)	1
CHA (1%)	3
AgSD + CHA (1% + 1%)	5
Ag Carbonate + CHA (1% + 1%)	5

It is to be understood that the above-described embodiments are illustrative of the application of the principles of the invention. Numerous other arrangements, processes, or compositions may be devised by those skilled in the art without departing from the spirit and scope of the invention.

Claims

1. A method of preparing an infection-resistant surface, characterized by preparing a coating vehicle by dispersing a matrix-forming polymeric material selected from the group consisting of biomedical polyurethane, biomedical silicones, biodegradable polymers and combinations thereof, in at least one solvent therefor, incorporating at least one antimicrobial agent in the coating vehicle to form a coating composition, coating the surface with the coating composition, and drying the coating.

2. The method of Claim 1, characterized in that the matrix-forming polymeric material is biomedical polyurethane preferably at a concentration in the range of 1 to 10%.

3. The method of Claim 1, characterized in that the matrix-forming polymeric material is a mixture of biomedical silicone and a biodegradable polymer, preferably poly(lactic acid) at a concentration in the range of 0.2 to 2%.

4. The method of Claim 1, characterized in that the matrix-forming polymeric material is a mixture of biomedical silicone and biomedical polyurethane.

5. The method of any of Claims 1 to 4, characterized in that the solvent is selected from the group consisting of acetic acid, methyl acetate, dimethylacetamide, ethyl 2-pyrrolidone, N-(2-hydroxyethyl)-2-pyrrolidone, N-cyclohexyl-2-pyrrolidone, and combinations thereof.

6. The method according to any of Claims 1 to 5, characterized in that the antimicrobial agent is selected from the group consisting of silver and its salts, the biguanides, polymyxin, tetracycline, aminoglycosides such as tobramycin and gentamicin, rifampicin, bacitracin, meomycin, chloramphenicol, miconazole, quinolones such as oxolinic acid, norfloxacin, nalidixic acid, pefloxacin, enoxacin and ciprofloxacin, penicillins such as oxacillin and pipracil, nonoxynol 9, fusidic acid, cephalosporins, and combinations thereof.

7. The method according to Claim 6, characterized in that said silver salts are selected from the group consisting of silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine.

8. The method according to Claim 6, characterized in that the biguanide is a chlorhexidine salt and is preferably selected from the group consisting of chlorhexidine, acetate, chlorhexidine gluconate, chlorhexidine hydrochloride, and chlorhexidine sulfate.

9. The method according to Claim 6, characterized in that the antimicrobial agent is a combination of a silver salt and a biguanide, preferably a salt of chlorhexidine.

10. The method according to Claim 9, characterized in that the antimicrobial agent is a combination of silver sulfadiazine and a salt of chlorhexidine, preferably chlorhexidine acetate.

11. The method according to any preceding Claim, characterized in that the surface is a surface of a medical device such as a catheter, contraceptive, a condom, a medical glove, a wound dressing, a wound clip, an orthopedic implant, a suture, an arterial graft, or a hernia patch.

12. The method according to any one of Claims 1 to 10, characterized in that said surface is one intended to contact health care patients such as a surface of a bed pan, a table top, a patient bed, the surface of a surgical apparatus, or an operating room surface.

13. The method of any preceding Claim, characterized in that at least one antimicrobial agent is dissolved or suspended in the coating vehicle.

14. The method of any of Claims 1 to 12, characterized in that at least one antimicrobial agent is dissolved in a solvent which is miscible with the solvent for the matrix-forming polymeric material and which is

subsequently incorporated into the coating vehicle.

15. A method of preparing an infection-resistant surface comprising preparing a first coating vehicle by dispersing a biomedical polyurethane in a solvent therefor, and optionally from 0.2 to 2% polylactic acid, and incorporating therein at least one antimicrobial agent; preparing a second coating vehicle by dispersing a biomedical silicone in a solvent therefor preferably at a concentration of 0.5 to 5%; applying said first coating vehicle to the surface and allowing it to form an adherent first coating; and applying said second coating over said first coating to form a second coating adherent to said first coating.

16. The method according to Claim 15, characterized in that antimicrobial agent is a chlorhexidine salt, preferably chlorhexidine acetate, at a level in the range of 0.5 to 3% and silver sulfadiazine in an amount within the range of 0.5 to 5%.

17. The method according to Claim 15 or 16, characterized in that the first coating vehicle further comprises a biodegradable polymer.

18. An infection-resistant composition comprising a coating vehicle comprising a biomedical polyurethane in at least one solvent therefor and an antimicrobial agent.

19. A composition according to claim 18, characterized in that the antimicrobial agent is selected from the group consisting of silver and its salts, the biguanides, polymyxin, tetracycline, aminoglycosides such as tobramycin and gentamicin, rifampicin, bacitracin, neomycin, chloramphenicol, miconazole, quinolones such as oxolinic acid, norfloxacin, nalidixic acid, pefloxicin, enoxacin and ciprofloxacin, penicillins such as oxacillin and pipracil, nonoxynol 9, fusidic acid, cephalosphorins, and combinations thereof.

20. A composition according to Claim 18 or 19, characterized in that the antimicrobial agent comprises a combination of a silver salt such as silver sulfadiazine and a biguanide such as chlorhexidine acetate in an amount effective to provide sustained antimicrobial effects when the composition is applied to a surface as a coating and dried.

21. A method of impregnating expanded PTFE medical devices, particularly vascular grafts which comprise preparing a coating vehicle comprising biomedical polyurethane and a biodegradable polymer, preferably poly(lactic acid), in a solvent therefor, together with at least one member of the group consisting of chlorhexidine and its salts, and pipracil as antimicrobial agents, placing said graft in contact with the coating vehicle while under reduced atmospheric pressure, and drying the treated graft.

22. The process of Claim 21, characterized in that the coating vehicle contains 0.25 to 1% biomedical polyurethane, 0.25 to 1% poly(lactic acid), 1% chlorhexidine acetate and 3% pipracil in a solvent comprising 25% N-ethyl-2-pyrrolidone and 75% tetrahydrofuran.

23. An expanded PTFE vascular graft, a substantial proportion of the interstices of which contains a coating composition comprising, by weight, one part biomedical polyurethane, one part poly(lactic acid), one part chlorhexidine acetate, and three parts pipracil.

24. A method of preparing an infection-resistant medical device which comprises:

(a) preparing a mixture of mixture of silver or a silver salt such as silver sulfadiazine or silver carbonate and a biguanide; and

(b) applying said mixture to the surface of a medical device.

25. The method of Claim 24, wherein the mixture is affixed to the surface of the device.

26. The method of Calim 24, wherein the mixture is applied to the surface as a powder.

27. The method of Claim 24, wherein the mixture is applied as an ingredient of a polymeric coating.

28. A method of preparing an infection-resistant medical device which comprises:

(a) preparing a mixture of

(i) a substance selected from the group consisting of chlorhexidine and its salts; and

(ii) a silver salt selected from the group consisting of silver sulfadiazine, silver acetate, silver benzoate, silver iodate, silver laurate, silver protein, silver chloride, silver palmitate, silver oxide, silver carbonate and silver nitrate; and

(b) applying the mixture to the surface of a medical device.

29. A method of preparing an infection-resistant medical device which comprises:

(a) preparing a mixture of chlorhexidine acetate and silver sulfadiazine, in proportions by weight ranging from 1:9 to 9:1; and

(b) applying the mixture to the surface of a medical device, the mixture being present at a level on the surface to impart substantial antimicrobial activity thereto.

30. The method of Claim 29, characterized in that the mixture is present in a coating on the surface at a level in the range of 10 to 70% by weight.

31. A method according to Claim 24, which comprises:

(a) preparing a powdered mixture of

(i) a member of the group consisting of chlorhexidine and its salts; and

(ii) a silver salt selected from the group consisting of a silver salt selected from the group consisting of silver sulfadiazine, silver oxide, silver carbonate and silver nitrate, silver acetate, silver benzoate, silver iodate, silver laurate, silver protein, silver chloride, silver palmitate;

(b) treating a surface of a medical device to render it at least slightly adhesive; and

(c) applying said powdered mixture to the surface of the medical device in a manner to cause adhesion to the powder thereto.

32. A method according to Claim 31, characterized in that the medical device is a glove, such as a latex

glove.

33. The method of Claim 32, where the glove is a thermoplastic latex and characterized in that the powder is applied to the glove at a point in the manufacturing process where the glove surface is soft, whereby the power particles adhere to the glove surface.

34. A method according to Claims 31, 32 or 33, characterized in that the mixture is applied by spraying a dry powdered mixture of dusting powder, a silver salt, and a biguanide.

35. A method according to Claim 31 or 32, characterized in that the mixture is applied by dipping the device into an aqueous or alcoholic slurry of dusting powder, a silver salt, and a biguanide.

36. A method of imparting infection-resistance to medical devices comprised of expanded PTFE materials comprising the step of applying to the device a coating vehicle comprising a biodegradable polymer, a silver salt and a biguanide.

37. A method of coating medical devices comprised of expanded PTFE materials to impart infection-resistance thereto comprising the steps of first dipping the device into a suspension of sodium sulfadiazine, chlorhexidine acetate and biodegradable polymer in alcohol-tetrahydrofuran (10:90), followed by a second step of dipping the device into alcoholic silver nitrate solution.

38. The method of Claims 1, 3, 4 or 15 to 17, characterized in that the coating vehicle comprises a room temperature-curing biomedical silicone.

39. The method of Claim 1, 3, 4 or 15 to 17, characterized in that the coating vehicle comprises a mixture of a polydimethyl siloxane medical adhesive and a silicone fluid comprising an amino functional polydimethyl siloxane copolymer and mixed aliphatic and isopropanol solvents.

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(54) Infection-resistant compositions, medical devices and surfaces and methods for preparing and using same.

(57) A method of preparing an infection-resistant medical device comprising one or more matrix-forming polymers selected from the group consisting of biomedical polyurethane, biomedical silicones and biodegradable polymers, and antimicrobial agents, especially a synergistic combination of a silver salt and chlorhexidine (or its salts); also disclosed are medical devices having the synergistic composition therein or compositions thereon.

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EUROPEAN SEARCH REPORT

Application Number

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X Y	EP-A-0 190 504 (JOHNSON MATTHEY) * Page 6, lines 11-19,21-26; page 8, lines 15-18; page 12, line 16 - page 13, line 6; claims *	1-3,6-7,11,13,15,18-19 8-10,16,20,29-31	A 61 L 29/00 A 61 L 31/00 A 61 L 27/00 A 61 L 15/03 A 61 L 17/00
Y	JOURNAL OF APPLIED BACTERIOLOGY, vol. 45, 1978, pages 397-405, The Society for Applied Bacteriology; L.B. QUESNEL et al.: "Synergism between chlorhexidine and sulphadiazine" * Page 401, last paragraph - page 404 *	8-10,16,20,29-31	
A	EP-A-0 207 624 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) * Claims * & US-A-4 612 337 (Cat. D)	36-37	
A	WO-A-8 602 006 (BAXTER TRAVENOL)		TECHNICAL FIELDS SEARCHED (Int. Cl4)
A,D	US-A-3 987 797 (M. STEPHENSON)		A 61 L 29 A 61 L 31 A 61 L 27 A 61 L 17 A 61 L 15
E	WO-A-8 904 674 (BIOCON OY) * Claims *	1-11	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	08-05-1990	COUSINS-VAN STEEN G.I.L.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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